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*Textbook*  
*of*  
**ORGANIC  
CHEMISTRY**

By F. WERTHEIM

Professor of Organic Chemistry  
in the University of Arkansas

Second Edition



THE BLAKISTON COMPANY  
Philadelphia                      Toronto

SECOND EDITION

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"All Science is formed necessarily of three things: the series of facts which constitute the science; the ideas which they call forth; the words which express them."

LAVOISIER.

"The contemplation of things as they are, without substitution or imposture, without error or confusion, is in itself a nobler thing than a whole harvest of inventions."

BACON.

"Through doubt we come to investigation and through investigation to the truth."

ABELARD.

"Science and peace will triumph over ignorance and war."

PASTEUR.

"Man is the interpreter of nature . . . Science the right interpretation."

WHEWELL.

"There is nothing so powerful as truth, often nothing so strange."

DANIEL WEBSTER.

"The first and the last thing required of genius is the love of truth."

GOETHE.

"Science is essentially a collective endeavor that owes its progress to the efforts of a multitude of workers in all periods and of all nationalities, who by common agreement are associated in the search for truth and its application to the improvement of the conditions of man."

GOETHE



## *Preface to the Second Edition*

The general scheme underlying the preparation of this book and the purposes which the book aims to fulfill are outlined in the preface to the first edition. The same ideas have motivated the writing of this second edition. Revision has given the opportunity to change the order of certain of the chapters and to shift several topics from one chapter to another. It is believed that these changes will facilitate the use of the book.

The text material has been brought up to date; certain aids to instruction have also been added. These comprise new tables, charts, and pictures of molecular models, also additional review questions and a number of numerical problems.

The author is grateful to Dr. J. W. Ferguson, Dr. E. Emmet Reid, and Dr. M. D. Soffer for information which has been helpful in preparation of this edition. Especial thanks are due to Dr. Austin M. Patterson who has offered many valuable suggestions. Further suggestions for improvement or notice of omissions or of any errors in the present volume will be gratefully received by the author.

E. WERTHEIM.

FAYETTEVILLE, ARKANSAS,



## *Preface to the First Edition*

This book presents material for a two semester beginning course in the theory of organic chemistry. It is intended to serve the needs of students who will major in chemistry or specialize in organic chemistry, also of those who are enrolled in premedical or chemical engineering courses.

In its preparation the ideas of clarity, directness, convenience, and adaptability have been stressed. If we accept the fact (stated very succinctly by Remsen in his text) that there are a "good many" compounds to be studied and a "good deal" of theory and much beside, it becomes a duty to smooth the path in every possible way.

To this end the usual detailed descriptions of individual compounds with their physical constants have been omitted. Descriptions of physical properties are given for whole series rather than for the individual compounds; physical constants are given in tabular form. These tables are quite complete and furnish ample data for the plotting of graphs. Statements referring to syntheses, reactions, uses, are so grouped as to facilitate the use of the book.

A table of melting points and boiling points has been incorporated in the appendix. This table should serve somewhat the purpose of a handbook in the laboratory; an advantage of this method is that but one reference is required to obtain these constants and other information, since the table is keyed by cross reference to the body of the text. The inclusion of this material makes students use the text during the laboratory period more than they otherwise would.

The book endeavors to present the salient facts in as direct and concise a manner as possible. The important relationships between compounds and reactions have been emphasized by cross reference and the use of as much repetition as seemed desirable. Charts and summaries have been freely employed in the effort to aid the initial study and facilitate review. Correct graphic formulas are used to a fuller extent than has been customary, since they have great teaching value. For the same reason, equations are repeated if they can be shown in different forms or with new implications. Suggestions for methods of study and review are given in several places. These have shown their effectiveness in the author's classes for some years.

The literature references are confined to the books and journals which would most probably be on hand in any school. Quite intentionally the journal references have been directed mainly to the publications of the American Chemical Society. The author believes that the student majoring



in chemistry gains decided benefits from an early introduction to the journals of the Society, not the least of which are his sense of orientation and desire to identify himself with this body. The more difficult articles and reviews are intended for the use of the instructor or students of very exceptional ability.

The "Review Questions" are such as have been used and found satisfactory for review and teaching purposes. Somewhat more than the usual number have been supplied.

To enlist the interest of the medical students there is a reasonable amount of reference to the medical uses of various compounds and to the biological connections of organic chemistry, also additional material on digestion, metabolism, and chemotherapy. Frequent use of sales data helps to make the book interesting and to remind the chemical engineers that organic chemistry deals with large amounts of materials and money.

Matter relating to the Friedel-Crafts reaction, Grignard reaction, Strain Theory, Optical Activity, Vitamins, Hormones, etc., is discussed in short individual chapters. The author has felt that the advantages of this method more than outweigh the drawback of the slight amount of repetition which it incurs. For shorter courses some of these chapters may well be omitted.

Organic chemistry as we know it today is the product of human brains and human hands. It gains in interest when the human element is recognized and at times emphasized in teaching. Nor does this treatment add to the burden of memorization. Every teacher of experience knows that facts "stick" better when coupled with an anecdote or interesting bit of history. There seems, then, to be full justification for the use of a little of the available space for the pictures of some of the builders of our science and for the historical tables to be found in the appendix and in certain selected chapters. It is easy to use this material to enliven the lectures if the teacher so elects, or it may be left to do its work unassisted. The biographies are purposely brief, but in most cases a reference in English is given to encourage further reading.

Work on this book began about fifteen years ago; there have been two mimeographed editions, hence the material has been revised on two occasions. The original title "Manual of Organic Chemistry" brought forth some criticism and in view of this and the present size of the volume a less controversial title has been adopted. To those who have used the previous books and offered their advice and criticism the author expresses his sincere thanks. The kindness of readers in reporting mistakes or omissions will be very much appreciated.

E. WERTHEIM.

## *Acknowledgments*

In the preparation of this book every available text and journal has been used; the number of these is too large to allow adequate recognition, if indeed it were still possible to assign the proper credit. A partial tally of the books consulted is given in the reference lists.

I am grateful to Dr. H. E. Howe, Dr. Arthur B. Lamb, Dr. Otto Reinmuth, and Dr. Gerald Wendt, Editors of the publications of the American Chemical Society, for permission to make adaptations of material in these journals and to copy illustrations. I wish to thank those chemists who have allowed the use of their pictures in the book.

I am indebted to Dr. R. E. Oesper for the loan of several pictures and am under especial obligation to Dr. F. B. Dains who allowed me the use of photographs from his private collection.

The following concerns supplied electrotypes: Fisher Scientific Co., figure 33; Sargent and Co., figures 2, 31, 48; du Pont Co., figures 61, 62. Photographs were supplied by Atlas Powder Co., Commercial Solvents Corporation, Fisher Scientific Co., B. F. Goodrich Co., Rohm and Haas Co., Shell Development Co., and Standard Oil Company of Indiana. Grateful acknowledgment is made to all of these concerns for their willing and generous cooperation.

E. WERTHEIM.



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**PART I**  
**ALIPHATIC COMPOUNDS**



## CHAPTER I

### INTRODUCTION

Until well into the first quarter of the nineteenth century all chemical substances were classified under two grand divisions, inorganic and organic. The inorganic or mineral compounds, whose chemistry was fairly well understood at the time, were obtained from lifeless materials under definite conditions which could be controlled in the laboratory. On the other hand, organic compounds were the products of living organisms, plant or animal. They were believed to be elaborated under the influence of the "vital force," i.e., the same force which was responsible for the growth of the plant or animal. Hence one could no more hope to understand how such compounds were made than he could expect to know the meaning of life itself. No attempts were made to synthesize such chemical compounds in the laboratory, because it was believed impossible to duplicate the results of the "vital force." The compounds were called organic because of their production by the organized cells of living matter.

However, in 1824, the chemist Wöhler was able to form from purely inorganic salts the substance urea, which had long been known as a product of human metabolism and a normal component of the urine. This crucial (and accidental) discovery marked the beginning of the overthrow of the theory of "vital force." Before long many other equally striking syntheses of organic substances had been performed in the laboratory. Through these experiments it was found that organic compounds obey the same general laws in their formation that hold for the inorganic compounds.\*

While we still classify compounds as inorganic and organic, our conception of organic compounds is entirely different from that which was held before Wöhler's synthesis. Today the laboratory synthesis of naturally-occurring substances occasions no surprise. We have seen synthetic indigo replace that formerly obtained from the indigo plant, and alizarin supplant the dye previously made from the madder root. In each case a natural substance was made more cheaply and in purer form by artificial means. In recent years a number of vitamins and hormones have been isolated, and the organic chemist has been asked to determine their structures and to synthesize them. The work has been highly successful. Meanwhile searching study of certain alkaloids has resulted in the prepara-

\* Wöhler's synthesis is shown on page 269. The result of the experiment was so contrary to the chemical thought of the time that Wöhler repeated the work many times to convince himself of the accuracy of his observation, and he did not publish the result for four years (see page 250).



tion of compounds having their curative effects but lacking some of their dangerous and unpleasant features. Nature has often been surpassed by the organic chemist, whose creations are of course subject to change and improvement, whereas the natural products are unvarying.

The number of synthetic organic compounds described in lexicons and journals has now reached many hundreds of thousands, and new substances are continually being evolved. Many of these synthetic compounds may be obtained from nature, while numbers of others have no such ties. All are, however, related in a simple way to compounds of natural origin and will always be called organic compounds because of this relationship. It has, moreover, been found that natural organic compounds contain carbon together with hydrogen, the other elements present varying in individual cases. Organic chemistry, therefore, may now be defined as the chemistry of the hydrogen compounds of carbon with their derivatives.\* Though all of these substances contain carbon, their study if included with that of the element carbon in general chemistry would throw the subject out of balance.† The importance of the organic compounds and certain differences in behavior between inorganic and organic compounds, as well as the vast scope of this branch of the chemistry of carbon therefore makes a separate treatment desirable.

It must again be noted that the laws which were found to govern reactions in general chemistry (law of conservation of mass, law of mass action, etc.) will hold with equal force in the domain of organic chemistry. In the following chapters the behavior of organic compounds is presented, beginning with the more simple substances. Later developments will present the derivatives of these simpler compounds and will bring out the network of relationships which exists between the various substances. As a preliminary to this study we will first consider the scope of the field to be covered and the methods by which organic compounds are analyzed and their formulas determined.

### SCOPE OF ORGANIC CHEMISTRY

The list which follows shows briefly some of the contacts of organic chemistry with daily life. As there is no department of life which is not directly influenced and helped by the applications of organic chemistry, this list is merely suggestive and is in no sense complete.

Relation to health.....	Study of composition of foods.
	Study of digestion.
	Study of action of drugs in the body.
	Preparation of new remedies.
	Preparation of disinfectants, anesthetics, antiseptics, vitamins, hormones.

\* The name "Organic Chemistry" was first used in the year 1800 by Novalis.

† Simple compounds, such as carbon dioxide, carbon disulfide, etc., are usually taken up in texts on inorganic chemistry.

## Relation to daily living

Heat.....	Fuel (oil and gas).
Light.....	Illuminating oils.
Food.....	Artificial coloring, sweetening, flavoring. Chemically prepared food. Cellophane protection.
Transportation.....	Gasoline and oil; antiknock fuel, rubber tires, plastics.
Comfort.....	Applications of textile chemistry; artificial leather.
Esthetic values.....	Applications of dyes; perfumes; soaps.
Miscellaneous*.....	Moving picture film, photographic developers, artificial ivory, insulating material, writing inks, lacquers and finishes, synthetic fibers and fabrics, cellophane, plastics and resins, explosives, detergents, paper.

A fairly large proportion of the national income is invested in organic chemical products, as will be evident from an inspection of the following table.

TABLE 1.—U. S. A. SALES OF ORGANIC CHEMICAL PRODUCTS (1939)  
(Values in millions of dollars)

Chemicals (not listed elsewhere) (1937).....	932
Coke and by-products.....	342
Corn syrup, oil, sugar, starch.....	91
Cottonseed oil, cake, meal, etc.....	171
Cotton goods.....	1,168
Dyes (1940).....	76
Disinfectants, insecticides.....	37
Explosives.....	71
Glue and gelatin.....	34
Leather and leather products.....	1,389
Linoleum (1937).....	35
Paper and pulp.....	1,160
Perfumes, cosmetics, etc.....	147
Petroleum refining.....	2,461
Rayon, allied products.....	247
Resins and plastics.....	78
Rubber tires and tubes.....	581
Soap and glycerol.....	308
Sugar, beet and cane (1937).....	531
Wood distillation products, charcoal.....	21
Synthetic organic chemicals (not of coal tar origin) (1940).....	226

The contributions of organic chemistry take several forms: (1) through organic industrial processes a natural product is made more suitable for general use. Examples of this are found in the refining of petroleum and of cane sugar. In somewhat the same connection we think of the preparation of rubber for its multiform uses. Other examples will be noted later. Some of our largest industries are engaged with these processes. (2) A

\* The National Resources Committee reported in 1937 those thirteen technologies which will have major economic importance in the next few decades. Four of them are organic chemistry projects: (1) Synthetic-rubber, (2) Plastics, (3) Artificial textile fibers, (4) Gasoline from coal. A fifth, prefabricated houses, will probably make strong demands on the resources of organic chemistry.

natural substance is studied until its internal structure and make-up is perfectly known, after which it is artificially made. Among the numerous examples of this application of organic chemistry are the preparation of oil of wintergreen, oil of bitter almonds, camphor, indigo. (3) Often through research a totally new compound never present in nature is applied to the enrichment of life. Substances such as saccharin, bakelite, salvarsan, phenacetin, aspirin, veronal, chloretone, may be cited from the large and ever-lengthening list of such wholly synthetic materials. Saccharin is used as a sweetening agent, being many hundreds of times as sweet as cane sugar. Veronal and chloretone belong to the class of drugs known as hypnotics, i.e., they induce sleep. Phenacetin and aspirin are of value in combating fever and headaches, while salvarsan has had marked success in the treatment of syphilis. Bakelite has many applications, being used for pipe stems, radio, automobile and aeroplane parts, fountain pen barrels, ornaments, laminated sheets, etc.

#### SOURCES OF ORGANIC COMPOUNDS

As stated above, a number of organic compounds are obtained directly from nature. These are of two kinds: either they are so complex that we do not yet know their exact make-up and so cannot synthesize them in our laboratories (at the present moment insulin is an example of such a compound), or else they are produced by nature much more cheaply than would be possible under factory methods. An example of the latter type is animal fat used for soap making and to yield glycerol.

Substances obtained from nature include alkaloids (quinine, morphine, strychnine, etc.), oils of seeds (cottonseed oil, linseed oil, tung oil), fibers (wool, cotton, silk), sugars, starches, cellulose, camphor, turpentine, and many other compounds and mixtures of compounds.

Nature supplies us with large deposits of petroleum, of coal, and of wood. The first named is a mixture of hundreds of organic compounds of different types. These are separated to some extent by the chemist, who then uses certain of them for synthetic purposes. Coal and wood, upon distillation, yield mixtures of compounds which may be separated and used for chemical synthesis. Coke with lime gives calcium carbide from which we get acetylene, a very important raw material.

At this time there is great interest in the utilization of agricultural materials for the preparation of organic chemicals. A large-scale use of farm products as raw materials for chemical synthesis would benefit farmers by providing new outlets for their crops. In addition, if agricultural *waste* materials can be used in this way, it should be possible to produce chemicals from them at a low price to the great benefit of the ultimate consumer. Several examples may be given of work already accomplished under this plan. Oat hulls, a by-product of the manufacture of breakfast food, are used as a source of furfural (page 641). Power alcohol has been produced

from corn. A gas suitable for fuel may be made from cornstalks. A plastic may be made from coffee beans.

The soybean seems to offer considerable promise as a source material, also the artichoke. Soybeans are now used in the production of paints, glue, inks, linoleum, plastics, and "wool." A total of 464,000,000 pounds of soybean oil was put to chemical use in 1941.

Compounds which may be made by fermentation include: alcohol from molasses, citric acid from sugar, gluconic acid from glucose, fumaric acid from starch. Acetone, butyl alcohol, and ethyl alcohol are made by fermentation of starch (page 99). Lactic acid is obtained from molasses or lactose or starch, glycerol from glucose. Experiments with the Jerusalem artichoke have already given 25 gallons of alcohol per ton of tubers.

#### POINTS OF DIFFERENCE BETWEEN ORGANIC AND INORGANIC COMPOUNDS AND THEIR REACTIONS

The table below shows some of the points in which organic compounds and reactions are found to differ from the inorganic. Certain other differences will be apparent after further study of the subject; at this point it is sufficient to say that organic compounds appear to be less stable than inorganic, and that in their reactions those of the molecular type are more common than are ionic reactions.

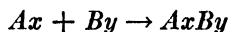
Organic	Inorganic
Compounds frequently of vivid or unusual color.	Possession of color not so frequent.
Compounds are low melting (under 400°). Often decomposed by heat.	High melting points (over 500°) quite common.
Natural compounds built from a few elements only.	Practically any element in the periodic system may take part.
Solubility in water often slight.	Easy solubility in water is common.
Easy solubility in organic solvents, such as ether, alcohol, etc.	Not usually soluble in the organic solvents.
Isomerism very common.	Isomerism not usual.
Compounds belong to many classes.	Most of the compounds studied are acids, bases, and salts.
Reactions generally complex, slow, non-ionic in character.	Reactions for the most part ionic and rapid. Reactions simple in character.
A large number of carbon atoms can be joined each to each in a molecule.	Number of atoms of any one element usually small and not joined each to each.

Reactions encountered in a study of inorganic chemistry are: (1) direct union, (2) substitution of one atom in a compound by another atom or group of atoms; (3) decomposition; (4) metathesis or double decomposition; (5) oxidation and reduction. Of these, type (5) has an unusual importance in organic chemistry. Also many reactions take place in the following manner: (6) two compounds unite to form an addition-product, which then parts with certain atoms to pass on to a final product more stable than the intermediate addition-product. Many examples of this type of reaction

will be found in the following pages (reactions of aldehydes, of ketones, the aldol condensation). Though this kind of reaction may occur with inorganic compounds, its great prevalence in organic chemistry, and the number of cases in which the intermediate compound may be isolated make this reaction unique for the organic branch.

The reaction may be illustrated in this way:

First step. Formation of addition compound,



Second step. Addition compound loses  $xy$ ,



Methods of making organic compounds involve the reactions mentioned above, also (7) replacement of an entire group within a molecule by another group or atom, and (8) rearrangement of the atoms of a molecule to a new structure.

## ELEMENTS IN NATURAL ORGANIC COMPOUNDS

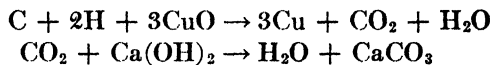
### *Qualitative Tests*

The organic compounds found in nature contain the following elements, which are here listed approximately in the order of their importance as "building blocks": carbon, hydrogen, oxygen, nitrogen, sulfur, phosphorus, metals (iron, calcium, magnesium, possibly others), halogens (iodine, bromine, chlorine). The vast majority of the synthetic compounds are also made up of the elements of this list, though other elements are sometimes included to obtain special properties (see page 602).

**Qualitative Tests.** Before making tests with a compound the chemist must be certain that it is pure. This will be shown in the case of a solid compound by the possession of a sharp melting point. The methods used to purify impure compounds are described in detail in the laboratory manual, and their underlying theory is considered further in the course in physical chemistry. For these reasons they are not included here. It will be well, however, to give a brief account of the qualitative and quantitative analysis of organic compounds because of the relationship of this work to the problem of formula construction. Full details for the actual experimental work will be found in the laboratory manuals.

**Tests for Carbon and Hydrogen.** When an organic compound is heated, it often happens that its carbon is more resistant to combustion than the other elements which it contains. The result is that the compound becomes black as it burns away, or as we say, it "chars." However, many organic compounds do not char when heated. We are thus in need of a more reliable test for the presence of carbon than is afforded by a simple heating. This is supplied by the following procedure, applicable to all organic compounds.

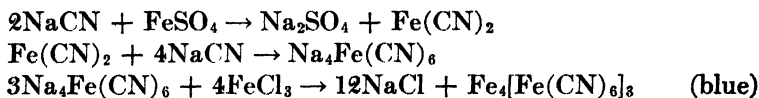
The compound is oxidized and carbon and hydrogen appear as carbon dioxide and water respectively. Copper oxide is generally used for the oxidation; the carbon dioxide is detected by the reaction with calcium hydroxide solution (lime water), the water by inspection. The equations follow:



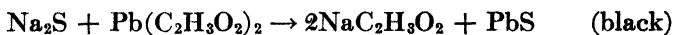
**Oxygen.** A compound containing oxygen is vaporized, the vapor being passed through glowing charcoal. Carbon dioxide is produced; this is detected by the fact that barium carbonate is precipitated when the gas is passed through barium hydroxide solution. "Ferric thiocyanate" gives a red color with certain organic compounds containing oxygen.

**Nitrogen, Sulfur, Halogens.** Since an organic compound cannot be depended upon to ionize in water solution, these elements to be detected must first be transferred to inorganic compounds. This may be accomplished by fusion of the sample with metallic sodium, which breaks it down to yield sodium cyanide, sulfide, and halide, respectively. We test for these according to the methods of inorganic qualitative analysis. Note that in the case of nitrogen the formation of the cyanide demands that the compound contain carbon. In the absence of carbon the cyanide could not form. The equations for the reactions concerned are inserted here for review:

*Nitrogen.*



*Sulfur.*



*Halogen.*



Halogen in an organic compound may often be detected by heating some of the compound on a clean copper wire in the Bunsen flame. The presence of halogen is shown by a green or blue flame, caused by the decomposition of the copper halide which has been formed. This procedure is known as the **Beilstein test**. A phosphorus-containing compound is fused with sodium carbonate-potassium nitrate mixture; the resulting phosphate is detected by the use of ammonium molybdate. A residue left after the ignition of a sample of an organic compound is analyzed for the presence of "inorganic" elements by the use of the usual methods of inorganic qualitative analysis.

## QUANTITATIVE ANALYSIS

**Carbon and Hydrogen.** As in the qualitative tests, the substance is oxidized by the use of copper oxide. A carefully weighed sample is placed at one end of a long tube of hard glass containing copper oxide, and while it is heated a stream of oxygen is passed over it. The vapor of the substance, mixed with oxygen, passes over the heated copper oxide, and the carbon dioxide and water produced are caught on their exit from the apparatus. The carbon dioxide is absorbed by a solution of potassium hydroxide or by Ascarite in a weighed container, while the water is taken up by granules of calcium chloride or by Dehydrite in a weighed drying tube. Each of these products is then carefully weighed and the percentage of carbon and hydrogen in the original sample is calculated from the weight obtained.\*

**Nitrogen.** For the determination of nitrogen a weighed sample of the compound is heated in the same type of apparatus used for carbon and hydrogen. All air (air contains about 79% nitrogen) is first expelled from the apparatus, its place being supplied by pure carbon dioxide. The vaporized substance passes over hot copper oxide and is oxidized, after which any oxides of nitrogen produced are reduced to nitrogen by passage over hot copper gauze. The issuing gases pass through a solution of potassium hydroxide which completely absorbs the carbon dioxide and water. The volume of nitrogen remaining is read off, after which a simple calculation leads to a knowledge of the percentage of nitrogen in the original sample. This method is called the absolute or Dumas method.

Certain compounds which yield their nitrogen as ammonia may be digested with concentrated sulfuric acid to form ammonium sulfate. At the close of the heating the mixture is made strongly alkaline, and the resulting ammonia is distilled into a measured amount of standard acid (taken in excess). The excess acid is estimated by titration with standard alkali thus giving knowledge of the amount of ammonia produced, and hence the percentage of nitrogen in the sample. This is called the Kjeldahl method; it is commonly employed in analyzing food products.

**Sulfur** is commonly determined by oxidizing the substance in a sealed tube with concentrated nitric acid (Carius method). The sulfur appears after the oxidation as sulfuric acid and is precipitated as barium sulfate. Substances, usually solids somewhat resistant to oxidation, may be oxidized in a metal bomb with sodium peroxide, the after-treatment being the same as for the Carius method.

**Halogens** are determined by a method similar to the Carius method for sulfur. Silver nitrate is placed in the tube with the sample, and on oxidation of the compound by the nitric acid, silver halide is produced. This is weighed for the determination of the percentage of halogen in the sample.

**Special Methods.** A more refined method of analysis involves catalytic oxidation in the presence of platinum. By placing several absorbing chemicals in sequence in the apparatus one may make analysis for several elements in one operation.

Much time is saved by the use of micro methods developed in recent years in which samples weighing only a few milligrams are analyzed. Such methods are also of especial value in dealing with rare compounds.

## ASSIGNING THE EMPIRICAL AND MOLECULAR FORMULAS

The result of a quantitative analysis of an organic compound is a knowledge of the relative weights of the various elements which it contains. For example, an analysis of a compound containing carbon, hydrogen, and oxygen might yield the following figures:

\* A few minutes of the laboratory time should be devoted to a visit to the combustion room for a demonstration of the combustion furnace and accessories.

Carbon.....	40.00%
Hydrogen.....	6.66%
Oxygen.....	53.34%

The percentage of oxygen is commonly obtained by subtracting from 100 the combined percentages of carbon and hydrogen, etc.

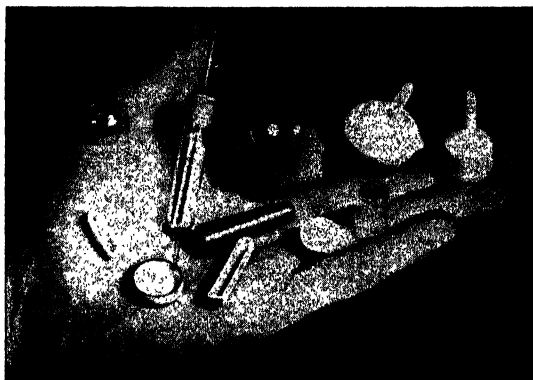


FIG. 1.—Apparatus used in microanalysis. (*Fisher Scientific Company.*)

While it is possible to make a quantitative analysis for oxygen, the method is not often employed.

To obtain an **empirical formula**\* from the percentage composition one divides such figures by the atomic weights of the several elements. Thus:

$$C \frac{40}{12} = C_{3.33}$$

$$H \frac{6.66}{1} = H_{6.66}$$

$$O \frac{53.34}{16} = O_{3.33}$$

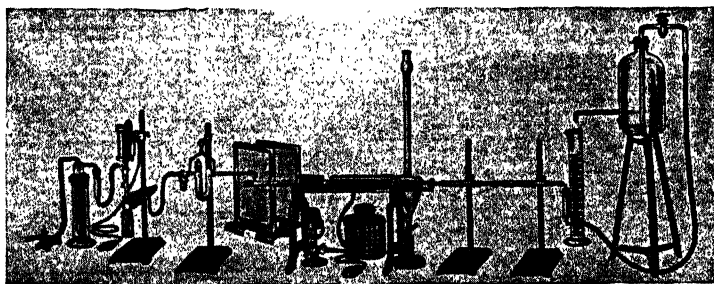


FIG. 2.—Electric micro combustion apparatus for determination of carbon and hydrogen.

The resulting formula,  $C_{3.33} H_{6.66} O_{3.33}$  shows the relative proportions of

\* This is the simplest formula possible; it shows only the elements and the simplest atomic ratio in which they exist in the compound.



the three elements in the compound, but cannot show the actual number of atoms of each element in the molecule until the subscripts are changed to whole numbers. Dividing each subscript by the smallest number gives us the empirical formula,  $\text{CH}_2\text{O}$ . The true or **molecular formula** of the compound in this instance may be  $\text{CH}_2\text{O}$  or it may be some multiple of this formula, since any multiple would have the same percentage composition. A knowledge of the molecular weight of the compound will enable the selection of the proper molecular formula. In this example a molecular weight of 30 would indicate  $\text{CH}_2\text{O}$ , while 60 would indicate  $\text{C}_2\text{H}_4\text{O}_2$  as the proper molecular formula.

### MOLECULAR WEIGHTS

The molecular weight of an organic compound is secured in various ways depending upon the nature of the compound.

(1) The compound is vaporized and from the weight of a known volume of the vapor the weight of 22.4 liters of the same at standard conditions is calculated. This latter weight, expressed in grams, is the molecular weight of the compound. (Victor Meyer and Dumas methods.)

(2) The compound is dissolved in a suitable solvent and the rise of boiling point of the solvent, or lowering of its freezing point is observed. The molecular weight is calculated from the formula:

$$M = \frac{1000 \cdot C \cdot w}{d \cdot W}$$

in which  $C$  is a constant depending on the solvent taken,  $w$  is the weight of substance used,  $W$  the weight of the solvent and  $d$  the rise in boiling point or the depression of freezing point in degrees centigrade. Compounds which undergo decomposition when heated alone may often be handled by this method, provided that a suitable solvent can be found. Solvents commonly used for freezing point determinations are: water, benzene, phenol, camphor; those often employed for boiling point determinations include water, acetic acid, ether, benzene.

(3) If the compound is an acid whose basicity is known, its silver salt may be analyzed and the molecular weight calculated from the percentage of silver therein. The silver salts of the organic acids have very slight solubility in water and are generally easy to prepare. When the dry salt is heated the organic elements are burned away, leaving a residue of pure silver.

(4) In some instances organic acids or bases may be titrated and the molecular weights calculated from the results obtained in this way. Further details with regard to the measurement of molecular weights may be found in textbooks and laboratory manuals of physical chemistry.

### REVIEW OF ATOMIC STRUCTURE

Before going on with the study of formulas it is desirable to consider the types of valence shown by various atoms, and in particular by carbon, which is the central atom in every organic compound. A preliminary rapid review of atomic structure will be of assistance.

The modern theory of atomic structure leads to the following conclusions:

(1) The atom contains a small compact nucleus. (2) Most of the mass of the atom is concentrated in the nucleus, which consists of protons\* and neu-

\* Proton. Positively charged hydrogen atom (same as hydrogen nucleus), mass  $1.67 \times 10^{-24}$  g.

trons,\* each type forming about half of the mass. (3) The positive charge of the nucleus, equal to the number of protons therein, is balanced by an equal number of electrons† which are arranged in concentric shells about the nucleus. (4) The number of extra-nuclear electrons (or the number of protons of the nucleus) is the **atomic number** of the element. (5) That shell of extra-nuclear electrons nearest the nucleus is the K shell, the next outer shell is L, etc. (6) The K shell of hydrogen contains one electron; for other atoms the K shell contains two electrons. (7) The L shell may hold up to eight electrons; no electrons are taken into the M shell until the L shell has its full quota of eight. The maximum number of electrons in the outermost shell of any atom is eight. The following table gives the structures of some of the lighter atoms (those of the first three periods).

TABLE 2.—ELECTRON ARRANGEMENTS, HYDROGEN TO ARGON

Group of periodic table	Atomic number	Element	K shell	L shell	M shell
	1	H	1		
0	2	He	2		
1	3	Li	2	1	
2	4	Be	2	2	
3	5	B	2	3	
4	6	C	2	4	
5	7	N	2	5	
6	8	O	2	6	
7	9	F	2	7	
0	10	Ne	2	8	
1	11	Na	2	8	1
2	12	Mg	2	8	2
3	13	Al	2	8	3
4	14	Si	2	8	4
5	15	P	2	8	5
6	16	S	2	8	6
7	17	Cl	2	8	7
0	18	A	2	8	8

(8) The electrons of the outer shell are termed **valence electrons**. Their number and arrangement will determine the chemical behavior of the element. (9) Those atoms which normally possess completed electron shells (Helium, Neon, Argon, etc.) are extremely stable and show no tendency to go into reaction with other elements. (10) Hydrogen, which has but one K electron, thus reacts in such wise as to gain another electron and so fill the K shell. (11) Other atoms also **tend toward the arrangement of the inert gases**, that is, an arrangement with an outer group of eight electrons.

\* **Neutron**. Neutral particle of practically the same mass as the proton; it is a proton-electron pair.

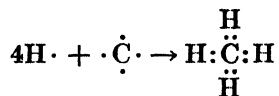
† **Electron**. Unit negative charge of electricity, mass about  $\frac{1}{1850}$  that of the proton.

(12) An atom may accomplish this either by capture of electrons from another atom with which it reacts (a tendency shown by elements of groups VI-VII of the periodic system), or by loss of its valence electrons in order to expose the completed underlying shell (tendency of elements of groups I-II).

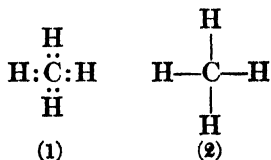
**Types of Valence Bonds.** The **electrovalent**, electrostatic, or **polar bond** is formed when an electron passes completely from the outer shell of one atom to that of another. For example, when sodium reacts with chlorine the one M electron of sodium is taken by chlorine to fill its M shell. The sodium atom becomes a positive ion, while the chlorine becomes a negative ion.  $\text{Na} \cdot + \cdot \ddot{\text{Cl}} : \rightarrow \text{Na}^+ : \ddot{\text{Cl}} :^-$ . The compound sodium chloride is thus composed of ions held to each other by the attraction of the opposite charges. In solid sodium chloride each sodium ion is surrounded by six chlorines and vice versa. In other words, no particular two of these ions could be singled out and called a molecule of sodium chloride.

In a **covalent bond** the atoms concerned *share a pair of electrons*, one of which has been contributed by each atom. This type of bond is very common in organic compounds. The shared electrons help to complete the outer octet of each of the atoms; thus each atom assumes a stable (inert gas) configuration, but without the formation of ions.

The formation of methane,  $\text{CH}_4$ , may be taken as an example. Here carbon with four valence electrons unites with four hydrogens, each having one valence electron. By the formation of four covalent bonds the carbon acquires its complete octet, while each hydrogen attains its K group of two electrons.



The covalent bond may be shown by printing the two electrons between the atoms (formula 1 below), but more commonly the atoms are joined by a line (formula 2). The symbols C and H stand for the **kernels** of the atoms (all of the atom save the valence electrons).



Carbon atoms readily share electrons with each other; thus organic compounds are based upon carbon chains, both branched and unbranched, and also rings of carbon atoms. The phenomenon of isomerism rests upon this fact.

## ISOMERISM

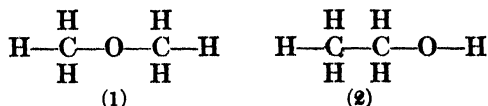
In our study of organic chemistry we shall frequently find several compounds of quite different chemical and physical properties built up of the same number of atoms of like elements, differing from each other only in their internal arrangement. In the study of general chemistry this phenomenon did not appear. The formula  $\text{H}_2\text{SO}_4$  stands for sulfuric acid, one compound; however for the formula  $\text{C}_4\text{H}_8$  there are eight compounds, for  $\text{C}_2\text{H}_4\text{O}_2$  there are four, while the formula  $\text{C}_{10}\text{H}_{16}$  stands for 195 different compounds. Compounds which have the same molecular formulas, but which differ from each other in properties, are called *isomers*, and the phenomenon is termed *isomerism*.\*

Isomerism is common among the organic compounds, and molecular formulas are not suitable in such instances, because one formula stands for all of the isomeric compounds and not any particular one of them. If these compounds which have the same composition and molecular weights are actually different, it *must* be because of differences of arrangement of their constituent atoms. In order to have distinct formulas for different isomers the organic chemist uses a device called a graphic formula, which attempts to picture the internal arrangement of the molecule. The organic chemist employs these graphic formulas in the same way that architects, contractors, and engineers use their blue-print drawings. Both the chemist and the engineer would be unable to work intelligently without such drawings.

## GRAPHIC FORMULAS

In studying general chemistry one finds many cases in which elements have variable valence; thus sulfur has a different valence in the compounds  $\text{H}_2\text{S}$  and  $\text{H}_2\text{SO}_4$ , and N has different valencies in the compounds  $\text{NH}_3$  and  $\text{HNO}_3$ . This confusion does not arise in the study of organic chemistry. Carbon in more than 99% of the compounds we shall study has a valence of four. Hydrogen is practically always monovalent, oxygen is divalent.†

Bearing these facts in mind one is able to set up formulas for compounds which tell more about them than can be shown by molecular formulas. For instance, suppose the molecular formula of a compound being studied (ethyl alcohol), is  $\text{C}_2\text{H}_6\text{O}$ . Following the above rules two different plans (and only two) may be made for the molecule, (1) and (2).



\* For large formulas the number of possible isomers is very large indeed. It has been shown, for instance, that the formula  $\text{C}_{40}\text{H}_{82}$  stands for 62,491,178,805,831 isomers. Only a few of these isomers have actually been made.

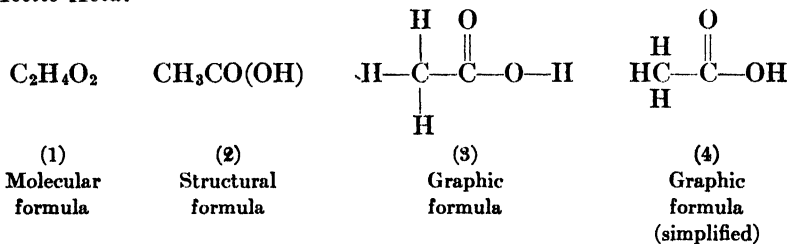
† The words *univalent* and *bivalent* are also used.

Tests of the compound in hand show that when it is treated with metallic sodium, one equivalent of hydrogen, and one only, is liberated and a new compound is formed. In other words one of the hydrogens in ethyl alcohol behaves differently from the others. This fact finds no expression in (1) in which all the hydrogen atoms are similarly situated, but (2) shows one hydrogen (on the oxygen atom) differently placed from the other five, all of which are joined to carbon. Other chemical reactions of the compound support this same formulation, which is therefore the correct plan for ethyl alcohol.

Another compound called dimethyl ether satisfies the other plan (1); these two compounds are therefore isomers.

Formulas such as the above are called graphic formulas. A structural or constitutional formula is often employed. This may be called a condensed graphic formula. It shows the relationships within the molecule, as does the former, but uses less space. The formulas for acetic acid printed below show the different ways in which a compound may be pictured.

*Acetic Acid.*

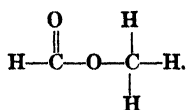


For the electronic formula, see page 171.

The molecular formula stands for three other compounds\* besides acetic acid, therefore it is not correct to use such a symbol in an equation to indicate acetic acid; when the graphic or structural formula is used there can be no ambiguity about the compound meant.

As illustrated above, the graphic formula of an organic compound is written in the manner already familiar from the course in general chemistry. Lines representing valence bonds are drawn between the atoms which are joined each to each, and the number of such lines proceeding from any atom must of course be equal to the valence of the atom.† It is satisfactory to

\* One of the isomers of acetic acid has the following graphic formula:



See if you can write the formulas for the other isomers.

† Lines may also be used in structural formulas:  $(\text{CH}_2-\text{CH}_2-\text{OH})$ , or dots may be employed  $(\text{CH}_2 \cdot \text{CH}_2 \cdot \text{OH})$ , or all indication of bonds may be omitted  $(\text{CH}_2\text{CH}_2\text{OH})$ .

omit some of these lines so long as this causes no confusion (see formula (4) above). As already stated (page 14) each line in a graphic formula represents two electrons shared by the two atoms concerned.

In formula (2) the three H's following the first C are attached to it, the oxygen coming next is joined to the second C, but the OH in the parenthesis is joined to the second C and not to the first O (if the OH were joined to the first O, the second C would have only a valence of two).

All of these formulas are written in two dimensions alone, and therefore they cannot show the true space relations existing in the actual molecule, which of course has three dimensions. In due time other types of formulas will be introduced which will show the space relations of the atoms and such formulas will be used when necessary.\* The flat "starfish" formulas are perfectly satisfactory in the majority of cases which arise, because we are usually not so much concerned with the space arrangements of the molecule as we are with its chemical behavior.

The structural formula† for a compound may be learned from a study of its reactions as has just been indicated. The opposite also holds. Certain groups, like hydroxyl, OH, amino,  $\text{NH}_2$ , and others which appear in many organic compounds, have reactions peculiar to the group. These reactions may be looked for whenever such groups are found in a compound; in this way the structural and graphic formulas, in which these groups and their relationships are plainly shown, form a key to the behavior of the compounds when one has learned to understand and read such formulas. Elementary organic chemistry is largely concerned with a study of groups such as those mentioned above, and the simpler compounds containing them. In this book structural and graphic formulas will be used as widely as is possible; the student should employ the graphic formulas from the very outset in writing equations. The various reactions will be much more rapidly and thoroughly mastered if this is done.

### METHOD OF STUDY

In learning the material of this (or any other) book you should read an entire chapter or assignment at a time in order to get a general idea of the topics which are described therein. Have pen and paper at hand and jot down the paragraph and divisional headings as you read; if the different sections have no headings supply these yourself. Copy important "key sentences" for headings. Following this, go over the same assignment one topic or division at a time. Lay the book aside and fill in a short summary for the first section studied. Proceed to the next division and after careful reading outline this as described above, if possible without any help from the book. Save your outline; when the entire assignment is finished use the outline to aid your memory in recalling what you have studied. The

\* For an example of a space model, see Fig. 7, page 29.

† The term structural formula is very often applied to what we here call a graphic formula.

various chapter outlines should be used again when you make a general review of the subject.\*

Answers to the questions and problems at the ends of the chapters of this book should be *written out* whether or not the instructor assigns this work to be handed in for credit. If there is insufficient time to do all of this work, choose representative questions and problems from the different types presented. *All* formulas used should be graphic. After the class has attained proficiency in the use of graphic formulas the instructor will permit the use of the structural formulas.

### REVIEW QUESTIONS

- For what reasons is organic chemistry studied as a separate branch of the science? How was "organic chemistry" defined in 1800 and how is it defined today?
- In what ways has the study of organic chemistry contributed to: (a) transportation? (b) the field of medicine? (c) improvements in textiles? (d) the electrical field?
- Name organic compounds used (a) as anesthetics; (b) as germicides; (c) as foods; (d) as substitutes for hard rubber or wood; (e) as hypnotics; (f) in lacquers; (g) as solvents.
- In what ways are organic compounds different from inorganic compounds?
- How do the reactions of organic compounds differ from those of inorganic compounds?
- A sulfur compound was analyzed by the Carius method. A sample weighing 0.2055 g. gave 0.3110 g. of barium sulfate. What percentage of sulfur did the compound contain? ( $\text{Et}_2\text{O}_2\text{SO}_2$ .)
- In a similar analysis a sulfur-containing compound gave 0.7119 g. of barium sulfate from a sample weighing 0.1895 g. What was the percentage of sulfur in the compound? ( $\text{EtSH}$ .)
- How much barium sulfate would be produced in the quantitative analysis by the Carius method of a 0.150 g. sample of an organic compound containing 37% of sulfur?
- An organic compound containing 13% of bromine was analyzed by the Carius method. The sample weighed 0.25 g. What weight of silver bromide should have been recorded in the analysis?
- A compound containing chlorine was analyzed by the Carius method. The sample weighed 0.1500 g. A precipitate of silver chloride weighing 0.4289 g. was obtained. What percentage of chlorine did the compound contain? ( $\text{MeCl}$ .)
- Calculate the empirical formulas of the following compounds from the percentage composition of the elements:
 

(a) C, 37.24	H, 7.76	Cl, 55.10	( $\text{EtCl}$ )
(b) C, 53.34	H, 15.56	N, 31.11	( $\text{EtNH}_2$ )
(c) C, 84.11	H, 16.00		
(d) C, 64.54	H, 9.09	O, 36.36	( $\text{PrCOOH}$ )
(e) C, 68.19	H, 13.64	O, 18.13	( $\text{AmOH}$ )
(f) C, 56.25	H, 3.9	O, 12.5	Cl, 27.34
- Calculate the percentage composition of the following:
 

(a)  $\text{C}_2\text{H}_6\text{O}$ ; (b)  $\text{C}_4\text{H}_{10}$ ; (c)  $\text{C}_2\text{H}_5\text{OCl}$ ; (d)  $\text{C}_6\text{H}_7\text{N}$ ; (e)  $\text{C}_4\text{H}_{11}\text{N}$ ; (f)  $\text{C}_4\text{H}_{10}\text{O}$ ; (g)  $\text{C}_3\text{H}_7\text{ON}$ .
- The molecular weight of a compound was determined by the Victor Meyer method. A sample weighing 0.1100 g. gave 24.16 cc. of gas measured over water at  $25.0^\circ\text{C}$ . The barometric height was 740.3 mm. (Vapor pressure of water at  $25^\circ$  is 23.5 mm.) What was the molecular weight of the compound? (Trichloromethane.)

\* See Manuel, "How to study chemistry." *J. Chem. Education*, 12, 579 (1935). The student is strongly urged to purchase G. F. Swain's excellent little book, *How to Study*, (McGraw-Hill Book Company, Inc.).

14. In a similar experiment a 0.200 g. sample gave 68.39 cc. of gas measured over water at 25.0°C. Barometric height was 720 mm. Calculate the molecular weight of the compound.
15. A sample of a substance weighing 4.200 g. dissolved in 100.0 g. of water caused a depression of the freezing point of 0.432°C. (The constant for water is 1.85.) Calculate the molecular weight of the substance. (A hexose.)
16. The freezing point constant of camphor is 40. In a given experiment 100 mg. of camphor (melting point 178°) was mixed with 10 mg. of "unknown." The mixture melted at 170°. What was the molecular weight of the unknown compound?
17. A sample of pure glucose weighing 0.150 g. was submitted to quantitative analysis. Calculate the increase in weight of the "Ascarite" and "Dehydrite" tubes.
18. A certain substance which contained carbon, hydrogen, and oxygen, upon analysis gave 0.6179 g. carbon dioxide and 0.1264 g. water from a sample weighing 0.2200 g. What is the empirical formula of the substance?
19. A sample of the above compound weighing 5.312 g. dissolved in 50.0 g. of alcohol raised the boiling point 1.300°C. (Constant for alcohol is 1.15.) What is the molecular formula for the substance?
20. Quantitative analysis of an organic compound gave the following results:
 

Weight of sample #1.....	0.200 g.
Weight of carbon dioxide.....	0.3887 g.
Weight of water.....	0.277 g.
Weight of sample #2.....	0.150 g.
Corrected volume of nitrogen.....	37.3 cc.

What is the empirical formula of the compound?
21. Quantitative analysis of an organic compound gave the following results:
 

Weight of sample.....	0.200 g.
Weight of carbon dioxide.....	0.550 g.
Weight of water.....	0.447 g.

Calculate the empirical formula of the compound.
22. A compound contains carbon, hydrogen, and oxygen. A quantitative analysis yields the following results:
 

Weight of sample.....	0.250 g.
Weight of carbon dioxide.....	0.595 g.
Weight of water.....	0.302 g.

What is the percentage of oxygen in this compound? 46.5
23. A certain compound was submitted to quantitative analysis. A sample weighing 0.2113 g. gave 0.6509 g. carbon dioxide and 0.3042 g. water. What is the empirical formula of the compound?
24. A compound which contained nitrogen gave the following figures upon analysis: The sample weighed 0.1960 g. and liberated 84.7 cc. nitrogen measured over water at 25.0°C. The barometric height was 740.0 mm. Calculate the percentage of nitrogen in the compound.
25. A compound contains 75% of carbon. What is the lowest molecular weight which can be assigned to it?
26. Calculate the percentage of nitrogen in dulcin; in caffeine; of sulfur in saccharin; of iodine in thyroxine.
27. An organic compound contains 53.34% of oxygen. What is the lowest molecular weight which can be assigned to the compound?
28. An organic compound contains 80% of carbon. What is the lowest molecular weight which can be assigned to the compound?



29. An organic compound containing C, H, and O, on analysis gave 0.2396 g. of carbon dioxide and 0.1305 g. of water from a sample weighing 0.1089 g. What is the lowest possible molecular weight of the compound?
30. Why is it necessary to heat an organic compound with sodium before attempting an analysis for chlorine or sulfur, bromine or phosphorus?
31. The silver salt of a certain monocarboxylic acid was ignited. A 0.2 g. sample of the salt gave 0.1293 g. of pure silver. What was the molecular weight of the acid?
32. What are the essential steps in the Kjeldahl analysis? In the Carius analysis for sulfur?
33. Explain clearly why space formulas for compounds have such great importance in organic chemistry.
34. Construct graphic formulas for the isomeric compounds having the formulas: (a)  $C_2H_4O_2$ ; (b)  $C_3H_6O_3$ ; (c)  $C_4H_8O_2$ . Note: Do not write formulas in which several oxygen atoms are joined together like this: O—O—O. Such arrangements do not commonly occur.
35. Would it be logical to rearrange the course of study so as to have organic chemistry precede inorganic chemistry? Give arguments for and against this plan.
36. Choose three organic compounds for examples. With these give illustrations for the following terms: (a) graphic formula; (b) structural formula; (c) empirical formula; (d) molecular formula.

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\* *Chem. Rev.* = Chemical Reviews.

*Ind. Eng. Chem.* = Industrial and Engineering Chemistry.

*J. Am. Chem. Soc.* = Journal of the American Chemical Society.

*J. Chem. Education* = Journal of Chemical Education.

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## CHAPTER II

### THE METHANE SERIES OF HYDROCARBONS

(*Paraffins, Alkanes*)

**Introduction.** The simplest organic compounds are built of but two elements, carbon and hydrogen. They are called **hydrocarbons**. They occur in nature and they can also be artificially formed by suitable methods. Not only do the hydrocarbons themselves find very important uses, but a number of them may be transformed to other chemical compounds of wide application. On the theoretical side it may be said that they are the parent compounds in the branch of chemistry which is taken up in this book. As will be explained very shortly, all the other compounds may be treated as derivatives of the hydrocarbons. For these reasons, i.e., the simplicity of their constitution and their relationship to other compounds, they will be studied first.

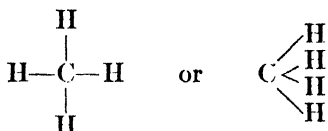
Those hydrocarbons, together with their derivatives which are taken up in the first half of this book, are called **aliphatic compounds**. In these compounds the carbon atoms are joined to each other to form open chains. The name aliphatic is conferred on these compounds because the natural fats belong to this series (Greek *aleiphar* = fat). In the second part of this book we shall study compounds in which the carbon atoms are joined to each other in the form of closed chains or rings (the aromatic compounds).

According to their chemical behavior the aliphatic hydrocarbons may be subdivided into several groups. One of these groups contains compounds which do not react readily at room temperature with acids, alkalies, or oxidizing agents. Because of this indifference the compounds of this series have been called **paraffins** (derived from *parum affinis*, Latin = small affinity). Ordinary paraffin wax is a mixture of several of these compounds. The simplest member of the paraffin series is called Methane or marsh gas, formula  $\text{CH}_4$ .

**Occurrence of Methane.** Methane is formed by the decomposition of organic material, such as dead leaves, in stagnant marshes, hence the name *marsh gas*. Also it occurs in coal mines, pockets of the gas being opened up during the process of mining. Here it is the cause of explosions (when mixed with air). It is called by the miners *fire-damp*. Methane is a constituent of coal gas, also of natural gas, and of petroleum. The digestion of certain types of food in the body leads to the production of methane, which may at times constitute as much as 50% of the intestinal gases. It is somewhat surprising to read the astronomer's report that methane is present in the atmosphere of Jupiter.

## MOLECULAR FORMULA OF METHANE

We have given the formula of methane as  $\text{CH}_4$ . To arrive at this molecular formula we know that we must first analyze the compound. One gram of methane when burned with oxygen will give 2.75 g. of carbon dioxide and 2.25 g. of water. A calculation shows that this indicates 75% of carbon and 25% of hydrogen. The empirical formula is then  $\text{CH}_4$ . As the molecular weight is found to be 16 the molecular formula is also  $\text{CH}_4$ . As a flat formula this may be written:



or in any other way, so long as the four hydrogens are shown to be joined to the carbon atom.

## SPACE FORMULA OF METHANE

The nature of the carbon atom was learned in the first year's work in general chemistry.\* Its atomic weight is 12 and its atomic number is 6. This means that the nucleus has a positive charge of 6 units, while 6 electrons are found outside the nucleus. Two of these are in the K shell and the remaining four valence electrons are in the L shell. These four valence electrons are pictured at the four corners of a regular tetrahedron (Fig. 3), that is they are shown as equidistant from each other and from the nucleus. When four points are so located with respect to a central point they will form the apices of a regular tetrahedron.

The letter C in the illustration stands for the kernel of the atom, in other words everything but the external shell of valence electrons. Now while it is probably true that all of these electrons are in constant motion, it is necessary for us to use a simpler conception in our work, and that shown here in which the electrons are fixed at the corners of a tetrahedron has been found the most successful.

You will remember that when two atoms come together without exchanging electrons each valence bond represents a pair of electrons shared between the two atoms. It will also be remembered that hydrogen tends to hold two electrons to its nucleus and that other atoms tend to hold eight electrons in their outer shells.\* The hydrogen atom has one proton and one electron, so that when four hydrogen atoms join to one carbon to give  $\text{CH}_4$ , each

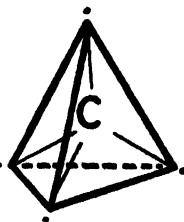


FIG. 3.

\* See page 12.

hydrogen is furnished with two electrons, while the carbon atom at the same time gets its complete octet (Fig. 4).\*

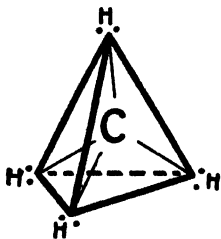


FIG. 4.

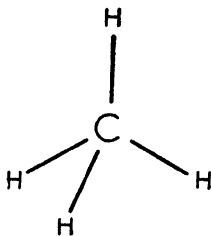


FIG. 5.

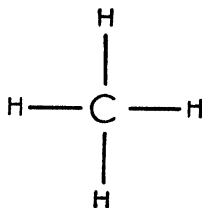


FIG. 6.

When this space model is projected upon the flat page we get the "starfish" arrangement of Fig. 5, which is generally written as shown in Fig. 6. The "starfish" formula is false in two respects: (1) it shows the molecule in only two dimensions; (2) it shows a  $90^\circ$  angle between the valence bonds, whereas the angle is actually  $109^\circ 28'$ . The convenience of this type of formula outweighs these objections. In looking at such a formula the student should try to visualize the tetrahedral model from which it originated and should bear in mind that each valence bond represents a pair of shared electrons.

**Physical Properties.**—Methane is a gas, colorless and odorless. It has but slight solubility in water, but is appreciably soluble in alcohol. Its specific gravity compared with that of air is only 0.554. As shown in Table 3 its boiling and melting points are both far below zero.

**Chemical Properties of Methane.** Towards acids, alkalies, and the ordinary reagents of the laboratory methane is practically inert. It burns in air with a slightly yellow flame, or may be exploded if mixed with oxygen in the proportion of one volume of methane to two volumes of oxygen. Mixtures of methane and air are explosive over the range from 5.8% methane to 13.3%. A mixture of one volume of methane and two volumes of chlorine is also explosive if exposed to direct sunlight. When means are taken to slow down the reaction, a mixture of chlorine derivatives of methane results. Carbon monoxide and hydrogen are produced when methane is heated with steam to about  $1000^\circ\text{C}$ . in the presence of activated nickel.

Ethane, propane, and other hydrocarbons are more reactive than methane. A study of their reactions in recent years has dispelled the previously held ideas which are implied in the class name "paraffin."

#### OTHER PARAFFIN HYDROCARBONS

The second member of the methane series,  $\text{C}_2\text{H}_6$ , is called Ethane. Like methane it is a gas, colorless and odorless. It is found associated with

\* In Figs. 3 and 4 the valence electrons are placed outside the tetrahedron so as to be plainly visible. Actually they lie closer to the central carbon atom.

methane in petroleum and in natural gas. Propane,  $C_3H_8$ , the next member of the series is also a gas. The names of some of the members of this series, together with their melting points, boiling points, and densities, will be found in the accompanying table. It will be seen that the compounds from pentane on are liquids. These are colorless and have but slight odor. The higher members of this series are solids similar in appearance to paraffin wax. These compounds occur in petroleum and are separated from it by the process of distillation. (See page 40.)

All of these compounds have but slight solubility in water, but they dissolve in the common organic solvents and they are mutually soluble, that is, they are miscible with each other.

TABLE 3.—PHYSICAL CONSTANTS OF NORMAL PARAFFINS

Name	Form- ula	M.p., °C.	B.p., °C.	Sp. g., at 20°/4°	Ht. of comb., Kg. cal./ mole	Calculated No. of isomers
Methane.....	$CH_4$	-182.5	-161.4	0.554 (air)	212.8	1
Ethane.....	$C_2H_6$	-183.2	- 89.0	0.374 <sup>15</sup> <sub>15</sub>	372.8	1
Propane.....	$C_3H_8$	-187.7	- 42.1	0.509 <sup>15</sup> <sub>15</sub>	530.6	1
Butane.....	$C_4H_{10}$	-138.3	- 0.5	0.584 <sup>15</sup> <sub>15</sub>	687.9	2
Pentane.....	$C_5H_{12}$	-129.7	36.0	0.626	845.3	3
Hexane.....	$C_6H_{14}$	- 95.39	68.72	0.659	1002.4	5
Heptane.....	$C_7H_{16}$	- 90.6	98.42	0.684	1150.8	9
Octane.....	$C_8H_{18}$	- 56.9	125.6	0.703	1306.8	18
Nonane.....	$C_9H_{20}$	- 53.7	150.7	0.717	1463	35
Decane.....	$C_{10}H_{22}$	- 29.7	174.0	0.730	1619.4	75
Undecane.....	$C_{11}H_{24}$	- 25.62	195.8	0.740	1775.3	159
Dodecane.....	$C_{12}H_{26}$	- 9.60	216.26	0.749	1932.4	355
Tridecane.....	$C_{13}H_{28}$	- 6.2	236.5	0.757	2110.5	802
Tetradecane.....	$C_{14}H_{30}$	5.5	253.5	0.763	2271.0	1,858
Pentadecane.....	$C_{15}H_{32}$	10.0	272.7	0.769	2415.4	4,347
Hexadecane.....	$C_{16}H_{34}$	18.14	286.5	0.773	2556.1	10,359
Heptadecane.....	$C_{17}H_{36}$	21.0	305.8	0.778	2743.2	24,894
Octadecane.....	$C_{18}H_{38}$	28.0	317.9	0.782	2903.2	60,523
Nonadecane.....	$C_{19}H_{40}$	31.4	336.2	0.786	3021.8	148,283
Eicosane.....	$C_{20}H_{42}$	36.7	355.0 <sup>15</sup>	0.789	3183.1	366,319
Docosane.....	$C_{22}H_{46}$	45.7	390.0 <sup>15</sup>	0.778 <sup>44</sup>	3491.4	
Tetracosane.....	$C_{24}H_{50}$	49.4	407.0 <sup>15</sup>	0.769 <sup>70</sup>	3863.3	
Hexacosane.....	$C_{26}H_{54}$	56.4	428.0 <sup>15</sup>	0.758 <sup>34</sup>	4161.4	
Octacosane.....	$C_{28}H_{58}$	60.3	446.0 <sup>15</sup>	0.776 <sup>70</sup>	4475.8	
Triacontane.....	$C_{30}H_{62}$	64.7	464.0 <sup>15</sup>	0.780 <sup>66</sup>	4793.9	4.1 × 10 <sup>9</sup>
Pentatriacontane.....	$C_{35}H_{72}$	74.5	481.0 <sup>2</sup>	0.773 <sup>34</sup>	5522.6	

**Uses of the Paraffins.** The presence of methane in natural gas and coal gas has been mentioned. About 3000 billion cu. ft. of natural gas (about

45–95% methane) were used in this country in 1941. About 450,000,000 gallons of liquefied propane and butane were used in 1941 as refrigerants and for heat and power in the home and in industry. Gasoline is a mixture of the lower liquid members of this series. Billions of gallons of gasoline are used yearly (about 26 billion in 1941) in automotive machinery; its use as a solvent is also important. Kerosene does duty as an illuminating oil and an insecticide; next higher members of the series are used in lubricating oils and greases. These heavy oils are also used as Diesel engine fuel. Vaseline includes semisolid members of the series. Its use in medicine and as a lubricant is familiar. Liquid petrolatum is a highly purified mixture of high-boiling hydrocarbons used as an intestinal lubricant. Paraffin wax is used in candles, as a waterproofing compound, as a lubricant, in the preservation of fruits and other food products (though certain bacteria can use it as food), as an ingredient of electrical insulation compounds, and in many other ways. The tarry residue of petroleum distillation is used for roofing and road-making material. The coke residue which is produced by high-temperature distillation is employed for the making of graphite electrodes and electric light carbons.

#### PREPARATION OF PARAFFINS

**Special methods for the preparation of methane** will be presented first.

(1) This compound may be formed in small amounts by the reaction of carbon and hydrogen at 1200°. This constitutes a synthesis directly from the elements.

(2) The following synthesis of methane may be termed an indirect synthesis from the elements:

(a) Carbon and sulfur unite to form carbon disulfide.

(b) Iron and sulfur unite to form iron sulfide.

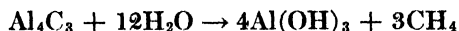
(c) By action of acid on iron sulfide, hydrogen sulfide is produced.

(d) Finally:

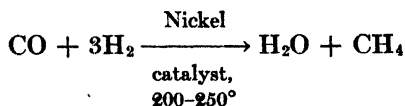


Berthelot first made  $\text{CH}_4$  by this method in 1856.

(3) By the action of water on aluminum carbide, methane is formed:



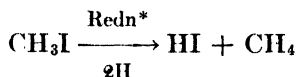
(4) The catalytic reduction of carbon monoxide in the presence of hydrogen produces methane:



This, again, is an indirect synthesis from the elements.

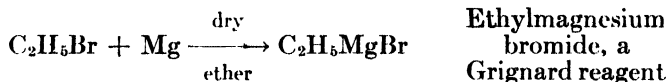
The following methods of preparation are general, that is, these methods will answer for the preparation of various members of the methane series.

(1) The reduction of a halogen compound of a hydrocarbon (called an alkyl halide) in the presence of hydrogen, leads to the formation of the hydrocarbon and halogen acid.



This reduction may easily be accomplished by the use of a zinc-copper couple, with which the alkyl halide dissolved in alcohol is brought into reaction. Other reducing combinations are: zinc and acid, sodium and alcohol. In some cases hydrogen iodide may be used. The latter method may be applied to alcohols and is shown on page 102.

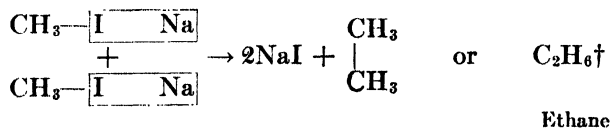
(2) Pure paraffins are very conveniently made from alkyl halides through the intermediate preparation of **Grignard reagents**. A Grignard reagent is formed by the interaction of metallic magnesium and an alkyl halide dissolved in dry ether.



Treatment of the Grignard reagent (in its ether solution) with water or a compound possessing active hydrogen (acid, alcohol, etc.) gives the free hydrocarbon.



(3) The reduction of an alkyl halide with metallic sodium (Wurtz reaction), gives a hydrocarbon with twice as many carbons as the alkyl halide employed and is a means of "stepping up" (increasing the length of a carbon chain).



Any reaction of this kind (or series of reactions) in which a compound is made from simpler compounds (perhaps from the elements) is called a **synthesis**. We shall see later (page 81) that the Wurtz reaction has limitations.

\* The reduction of a compound will be indicated in this book by "Redn" placed over the sign of reaction. The hydrogen atoms which are needed for the reaction may be supplied by action of an acid on a metal or in other ways, as the occasion may require.

† This reaction must be taken on faith for the present. The mechanism will be discussed in a later chapter.



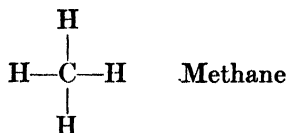
(4) Hydrocarbons of the methane series with short carbon chains may be made by heating the sodium salt of the corresponding acid (having one more carbon atom than the desired compound) with excess of a strong base. As an example take the preparation of methane; this hydrocarbon having but one carbon, the acid used must have two carbons (Acetic acid). Its sodium salt is to be heated with a strong base (NaOH, KOH) in the absence of water. The equation is given below:



Soda lime, a mixture of sodium hydroxide and calcium oxide, is used in this reaction. Presence of the calcium oxide tends to decrease the etching of the glass vessel. The  $\text{CH}_4$  is mixed with small amounts of other gases produced by side-reactions not shown here.

#### GRAPHIC FORMULAS. ISOMERISM

Carbon being tetravalent\* and hydrogen monovalent, it follows that the simplest hydrocarbon possible *must* have the formula  $\text{CH}_4$ . Its plan, already discussed, is shown below.



Compounds of this kind, in which every atom is held by one valence bond, are called **saturated compounds**. The hydrogen atoms are placed in equivalent positions about the central carbon atom, because experiment has shown that they are all related to this carbon in the same way.

For example: the chief reaction of compounds like methane is substitution. When treated with a free halogen, halogen acid is liberated, and hydrogen of methane is substituted by halogen:



It is conceivable that if the hydrogens had different relations to the carbon, several different compounds could result from this reaction, one hydrogen being replaced in one case, and another in another instance. However, it makes no difference how the above reaction is carried out, one and the same compound always results when one chlorine replaces one hydrogen. This proves that the hydrogens are equivalent.

**Models of Molecules.** Several types of molecular models are in common use. One type, built on the "Tinker-Toy" principle, has black wooden balls to represent carbon atoms. Other balls, variously colored, representing hydrogen, chlorine, etc., are attached to the carbons and to

\* Some use the word *quadrivalent*.

each other by means of wooden pegs which represent the valence bonds (see Fig. 7).

The Fisher-Hirschfelder models are built to scale from actual measurements of atomic radii and bond angles. The "atoms" from which they are constructed are 100,000,000 times the actual size, but are in fact quite small and the molecular models are very compact (see Fig. 8).

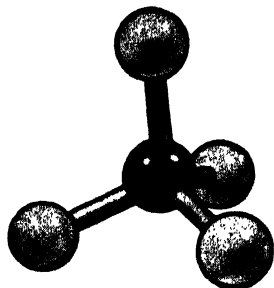


FIG. 7.



FIG. 8.

FIGS. 7, 8.—Models of Methane molecules.

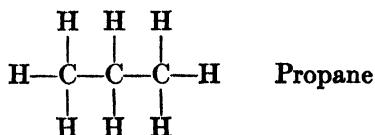
Such models are quite important in working out problems of structure, but in the classroom they are perhaps less often used than the Tinker-Toy models, since the latter can be seen more plainly from a distance. The student should understand that the Tinker-Toy models greatly exaggerate the interatomic distances.

When a saturated hydrocarbon has two carbons the formula is as shown below:

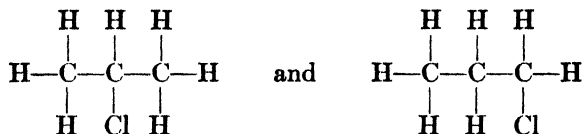


The compound is called ethane. Again the hydrogens are equivalent to each other in their relations to the carbon atoms, and experiment has shown that there is only one compound of the formula  $\text{C}_2\text{H}_5\text{Cl}$ .

The structure of a saturated hydrocarbon having three carbon atoms is as follows:

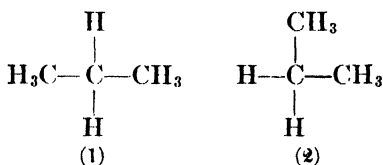


The hydrogens in this compound are evidently not equivalent; those on the central carbon atom have different environment from those on the end carbons. We would predict the existence of two different compounds of formula  $\text{C}_3\text{H}_7\text{Cl}$  and experiment has demonstrated that two such compounds actually exist, and only two:

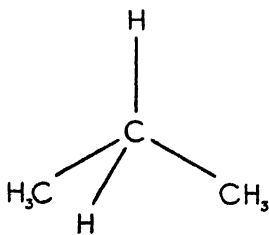


It is possible to tell from their reactions which formula to assign to each compound; this will be made clear in the ensuing sections. One sees at once the great value of the graphic formula which allows us to make predictions such as that just quoted. Chemists place implicit faith in these formulas because at no time in the history of organic chemistry has it been possible to make isomers of any compound in a greater number than that predicted from the graphic formula.\*

On inspection of flat formulas it might seem that there should be two kinds of propane as shown below, (1) and (2).

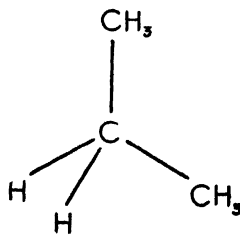


However if we use the space models we see that these formulas stand for but one compound, (1) and (2) below.



(1)

FIG. 9.

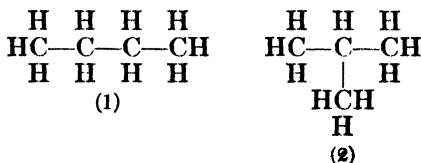


(2)

FIG. 10.

With a little practice one is able to view the flat formulas and see them in three dimensions, if they are simple. For complex formulas one resorts to the use of models when a knowledge of the actual structure in space is important.

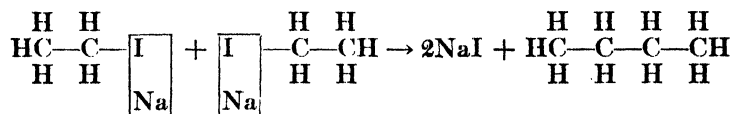
If we attempt to make a graphic formula for a hydrocarbon having four carbons, we find that two different structures are possible, (1) and (2).



Isomeric Butanes

\* See, however, page 332.

In (1) the carbon atoms are seen to be joined in a line, forming what we call a "straight-chain" compound, while in (2) there is a chain of three carbons bearing a fourth on its central member, the whole group forming a "branched-chain" compound. Now there are actually two different substances having this same molecular formula,  $C_4H_{10}$ . Their chemical reactions are slightly different, and they differ in physical properties. Thus one boils at  $-0.5^\circ$ , whereas the boiling point of the other substance is  $-11.72^\circ C$ . It is generally possible to distinguish between such isomers by a consideration of the methods used to make the compounds. Thus, if the Wurtz reaction (see p. 27) were carried out with such a compound as ethyl iodide, it is reasonable to suppose that a substance with the structure shown in (1) above would result.



When we carry out this reaction, the compound secured boils at  $-0.5^\circ$ . Therefore, the compound boiling at  $-11.72^\circ$  is presumed to have the structure shown in (2). There is other evidence which leads to the same conclusion.

#### REACTIONS OF THE PARAFFINS

As has already been said, the methane hydrocarbons are quite inert to the ordinary reagents of the laboratory. This is especially the case for low temperature reactions with the lower members having straight chains.

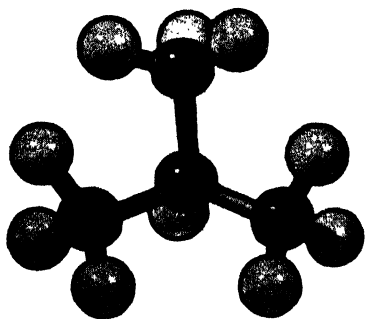


FIG. 11.

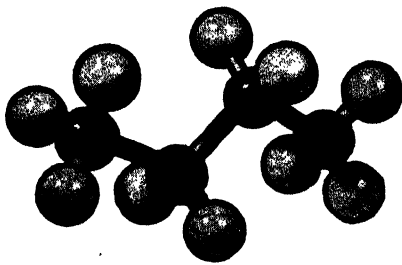
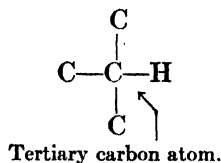
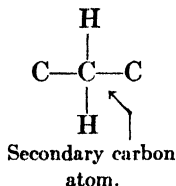
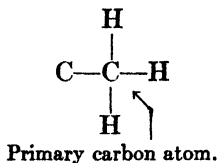


FIG. 12.

FIGS. 11, 12.—Models of butane molecules.

It is true that commercial mixtures such as kerosene and gasoline will appear to undergo reaction with nitric or sulfuric acid at room temperature, but this reaction is due to impurities, and quickly subsides when the latter are used up. In attempting substitution reactions one notes that the three types of hydrogen in the compounds are not replaced with equal ease.

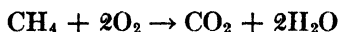
**Primary hydrogen** (that attached to a primary carbon atom) is least readily substituted; **tertiary hydrogen** (attached to a tertiary carbon atom) is most easily replaced. The ease of replacement of **secondary hydrogen** is intermediate. The diagram shows that a **primary carbon atom** is joined to one other carbon, whereas a **secondary carbon atom** is joined to two other carbons, and a **tertiary carbon atom** to three others.



The paraffins undergo reaction when they are superheated, when treated with a halogen, with fuming sulfuric acid, or with nitric acid (at 400°C.). They are easily burned in the presence of air or oxygen. Their reactions thus fall under the heads of oxidation, substitution, and pyrolysis.

(1) *Oxidation.* The products in this case are  $\text{H}_2\text{O}$  and  $\text{CO}_2$  for complete combustion.

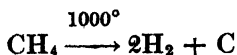
Example:



If insufficient oxygen is present methane may be burned to produce chiefly carbon monoxide and water.\* Other products result with a change of experimental conditions.

An important commercial application is the preparation of formaldehyde from methane by air oxidation; by-products include methanol and acetaldehyde. Another application concerns the catalytic air oxidation of petroleum fractions to give mixtures of acids, useful for preparation of soaps or esters.

(2) *Pyrolysis.* If methane be heated to about 1000°, the molecules fall apart. Such a decomposition is termed thermal decomposition or pyrolysis, and when larger molecules are concerned is usually termed "cracking." Molecular fragments may recombine to give ethane in good yield; aromatic compounds may also be formed in this reaction under suitable conditions. The following equation illustrates a special application:

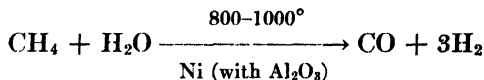


The reaction may be carried out commercially by burning natural gas with insufficient air. The heat of the flame promotes the reaction, and while some  $\text{CO}_2$  and  $\text{H}_2\text{O}$  are produced, the yield of free carbon is good. This

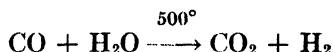
\* By careful regulation of the temperature and oxygen supply, and by the use of various catalysts, the saturated hydrocarbons may be incompletely oxidized to alcohols, aldehydes, acids, etc.

finely divided "carbon black" is used in (1) compounding rubber tires and in (2) paints.\* About 300,000,000 pounds a year (50% of total production) are used in rubber for tires.

Methane when heated with steam will yield carbon monoxide and hydrogen:



This is an important source of hydrogen for use in the Bergius process or for ammonia synthesis. Additional hydrogen is secured from the reaction of carbon monoxide and steam, using iron oxide-chromium oxide catalyst:

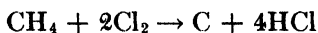


The cracking of saturated hydrocarbons is discussed further on page 54.

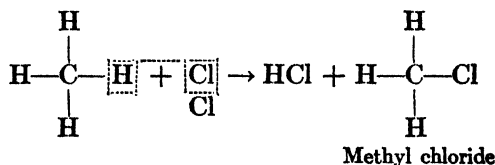
(3) *Substitution* (a) Sulfonation. Fuming sulfuric acid reacts readily with saturated hydrocarbons having tertiary hydrogen, but only slowly with the straight-chain compounds. The products are a sulfonic acid,  $\text{C}_n\text{H}_{2n+1} \cdot \text{SO}_3\text{H}$ , and water.

(b) Nitration. Saturated hydrocarbons nitrated in the vapor phase at  $400^\circ$  give nitro compounds (formula  $\text{C}_n\text{H}_{2n+1} \cdot \text{NO}_2$ ) and water. Chain cleavage occurs at the same time, so that a mixture of nitro compounds is secured in the nitration of a single compound (see page 297).

(c) Halogenation. In direct sunlight methane reacts with two volumes of chlorine with violence, to produce free carbon and hydrogen chloride:



In diffuse light, hydrogen in methane and other members of this series may be replaced by halogen atom, as shown in the following equation:



Note that this reaction yields a by-product, hydrogen chloride. Bromine reacts as shown above, but iodine does not take part in such a reaction with these hydrocarbons. As the halogen atom takes the place of hydrogen, it is said to have "substituted" the hydrogen. The reaction is called **substitution**, and the derivative† is known as a "substitution product" of methane.‡

\* See Ellis, *Chemistry of Petroleum Derivatives*, Chemical Catalog Co., 1934, p. 252.

† A derivative is a compound made from another compound by a simple chemical process.

‡ The reaction shown is "halogenation," one type of substitution; specifically this is "chlorination."

The number of hydrogens substituted in this way is a function of temperature, concentration, etc. By the reaction shown above, using excess chlorine, one could prepare the following compounds, by successive substitution of hydrogen of methane by halogen (see page 79).

$\text{CH}_3\text{Cl}$ .....	Chloromethane or Methyl chloride
$\text{CH}_2\text{Cl}_2$ .....	Dichloromethane or Methylene chloride
$\text{CHCl}_3$ .....	Trichloromethane or Chloroform
$\text{CCl}_4$ .....	Tetrachloromethane or Carbon tetrachloride

The student will note that each of these compounds has several names. This may seem an undesirable feature and an undue tax on the memory, but the contrary will prove true as our study in this subject advances, and the fact that the majority of the organic compounds can be named in several ways will be found a decided advantage.

**Radicals.** It will be noted that the first compound above has a name similar to that of an inorganic binary compound, i.e.:

$\text{KCl}$ .....	Potassium chloride
$\text{CH}_3\text{Cl}$ .....	Methyl chloride

The fact is that this compound may undergo a series of transformations in which the Cl-atom is changed for other atoms or groups of atoms, while the carbon and three hydrogens remain in a group unchanged. Some compounds made in this way are:

$\text{CH}_3\text{OH}$ .....	Methyl alcohol
$\text{CH}_3\text{CN}$ .....	Methyl cyanide
$\text{CH}_3\text{I}$ .....	Methyl iodide

Groups like  $\text{SO}_4^{=}$ ,  $\text{NO}_3^-$ , etc., which remain intact during different reactions of their compounds, we call **radicals**. Therefore  $-\text{CH}_3$  is also a radical; we call this the *methyl* group.

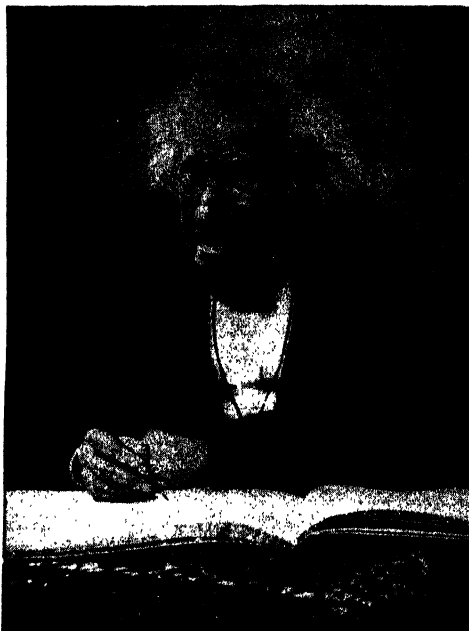
**Nomenclature of Radicals.** Names and formulas of a few simple radicals are given below. It is convenient to use these radical names when referring to parts of complex formulas. The names are formed by placing "yl" after the stem "meth" etc., instead of "ane."

$\text{CH}_3-$ .....	Methyl
$\text{C}_2\text{H}_5-$ .....	Ethyl
$\text{CH}_3\text{CH}_2\text{CH}_2-$ .....	Normal propyl
$(\text{CH}_3)_2\text{CH}-$ .....	Isopropyl
$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2-$ .....	Normal butyl
$\begin{array}{c}   \\ \text{CH}_3\text{CH}_2\text{CHCH}_3 \end{array}$ .....	Secondary butyl
$(\text{CH}_3)_2\text{CHCH}_2-$ .....	Isobutyl
$(\text{CH}_3)_3\text{C}-$ .....	Tertiary butyl
$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-$ .....	Normal amyl

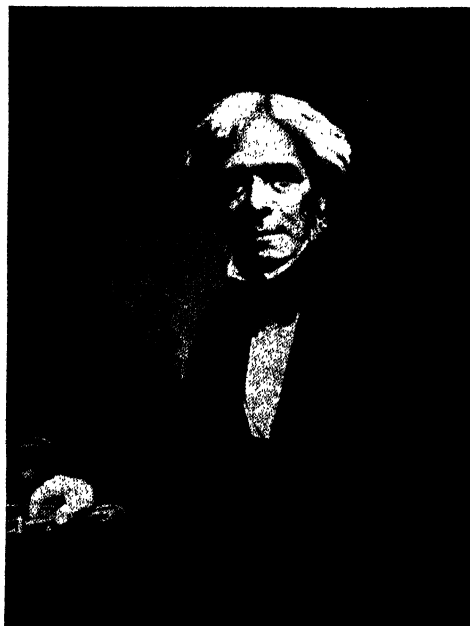
These radicals have the type formula  $\text{C}_n\text{H}_{2n+1}^*$  and are known as **alkyl**

\* See page 37.

MICHEL E. CHEVREUL. (1786-1889, French.) His work with fats and oils, begun in 1811, is outstanding. He called attention to the value of melting point and boiling point for the characterization of organic compounds. This picture, taken when he was 100 years old, is an early example of candid photography. See *J. Soc. Chem. Ind.*, **8**, 268 (1889), *Am. Chem. J.*, **11**, 289 (1889), *J. Chem. Soc. (London)*, **57**, 445 (1890).



*Piz.*



MICHAEL FARADAY. (1791-1867, English.) Faraday is best known for his work in the field of physics, but he made valuable contributions to organic chemistry. He first prepared halogen compounds (ethylene iodide, organic chlorides) and is famous for his extraction of benzene from oil gas. He proved the "isomerism" of ethylene and butylene. See *J. Soc. Chem. Ind.*, **44**, 630, 653 (1925), *Science*, **73**, 433, 462 (1931), *J. Chem. Education*, **8**, 1493 (1931); also this book, page 393.



**radicals** (because they appear in the alcohols). Abbreviations are often used: Me for methyl, Et for ethyl, Pr for propyl, etc.\* **The letter R stands for any radical**, thus the formula RH indicates a hydrocarbon.

### NOMENCLATURE OF COMPOUNDS

A simple and accurate system of nomenclature is of the greatest importance to the proper advance of the science of organic chemistry. The number of compounds already made and at the disposal of chemists is very large; thousands of additional compounds are added to the list every year. There is some difficulty in making such a system of naming, because it must be easily understood and not cumbersome, but at the same time comprehensive enough to provide for both the known compounds and those still unknown and yet to be made.

Coördinated efforts toward the construction of a system of naming organic compounds led to the congress of chemists in Geneva, Switzerland in 1892 from whose recommendations we have the "Geneva" system of nomenclature.† In 1922 the International Union of Chemistry set up a committee to care for the reform of the nomenclature. On this committee the important chemical journals of the world are represented by delegates. The meetings and deliberations of the committee resulted in the "Definitive Report" of 1930.‡

The I.U.C. nomenclature is used in this book, but older names are given as well, because they are still in daily use and will be encountered by the student in other books and in the journal literature. It is likely that for many simple compounds these older names will always be used, along with the new names.

Students sometimes experience a little difficulty in using the official naming system at the beginning of a course in organic chemistry, but ordinarily the main points are not hard to learn. One has to remember that this naming system is the only part of organic chemistry that man has himself created; of necessity it cannot be perfect.

### NOMENCLATURE OF THE PARAFFINS

The first four members of the series have special names:

Methane.....	CH <sub>4</sub>
Ethane.....	C <sub>2</sub> H <sub>6</sub>
Propane.....	C <sub>3</sub> H <sub>8</sub>
Butane.....	C <sub>4</sub> H <sub>10</sub>

From C<sub>5</sub>H<sub>12</sub> on, the names are founded on the Greek and Latin numbering systems thus:

\* Radicals higher than amyl (Am) are not abbreviated at present.

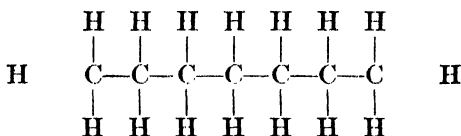
† For an interesting review of the meeting, see Armstrong, *Am. Chem. J.*, **15**, 50 (1893).

‡ See Patterson, Definitive report of the commission on the reform of the nomenclature of organic chemistry, *J. Am. Chem. Soc.*, **55**, 3905 (1933).

$C_5H_{12}$ .....	Pentane*
$C_6H_{14}$ .....	Hexane
$C_7H_{16}$ .....	Heptane
$C_8H_{18}$ .....	Octane
etc.	

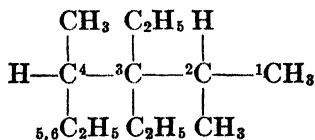
All of the compounds of this series have names ending in *-ane*.† Their formulas differ from one another by the constant difference  $CH_2$  as we go up or down the series. Such a series of compounds as this, in which the members are of the same chemical type, with formulas differing by  $CH_2$ , is called a **homologous series**. The members are called **homologs** of one another. All of the aliphatic compounds belong to such series, and this fact greatly simplifies the study of organic chemistry. Instead of taking up one by one the thousands upon thousands of known compounds, we are enabled to consider all of the compounds of any one homologous series at one time. These compounds have similar chemical traits, because their structures are closely related; therefore we can learn the chemistry of the entire group with no more effort than would otherwise be required to study a single compound. Of course we may anticipate certain "exceptions" to this general rule, but such exceptions will make very little trouble.

Inspection of the structure of any member of the methane series, say heptane for example:



shows that for each carbon there are two hydrogens, and in addition there are two more hydrogens for the ends of the chain. Thus we arrive at a *type formula* for the series,  $C_nH_{2n+2}$ , which stands for any one of the compounds of the series.

**How to Name a Complex Structure (I.U.C. System).** First, pick out the longest continuous chain of carbons which the formula contains. In the following example, the longest chain which can be found has six carbon atoms (hence this is a substituted hexane).

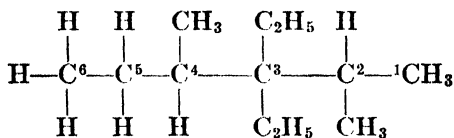


Next, number the carbons of this chain (the longest one) as shown above. Now starting at number one of the chain, see which groups have been substituted for hydrogen, noting in each case the number of the carbon

\* The five-carbon radical is not called pentyl, but instead the name *amyl* is used.

† They are often called *alkanes*.

atom on which the group is placed. In the present example, there is a methyl group on carbon two, two ethyls on carbon three, and methyl on carbon four. These various groups are substituted for hydrogen atoms in hexane, therefore the name of the compound is 3,3-diethyl-2,4-dimethylhexane. Rewritten to show more plainly that this is a substituted hexane, the formula looks like this:

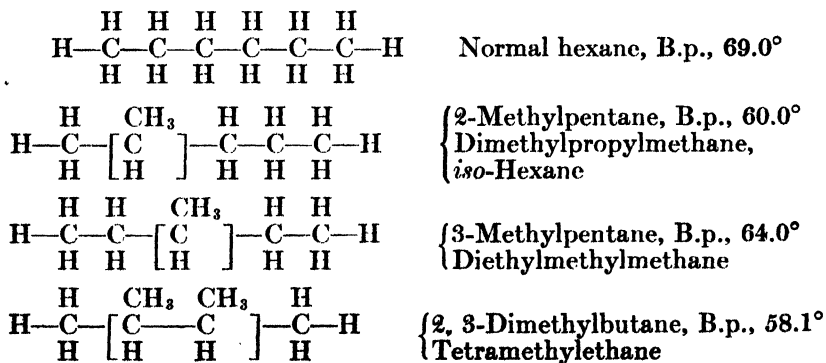


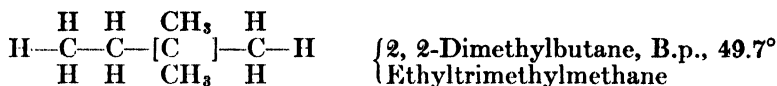
It will be seen that these two formulas are alike, even though one of them has been somewhat contorted (this is sometimes resorted to for greater ease in printing a book or for making certain equations easier for the eye). The numbering of the chain is always such that the numbers in the name are the *smallest possible*. If, in this case, we had numbered from left to right, the "rule of lowest numbers" would have been broken.

It is also feasible to name complex hydrocarbons as if they were derived from methane by the substitution of hydrogen by various alkyl groups. To apply this method choose as the central methane carbon atom that carbon in the formula which is attached to the largest number of other carbons. The examples below show the application of this system of naming to the hexanes.

When only two isomers of a saturated hydrocarbon occur, the one with straight chain is called *normal* (*n*), the other *iso*; when more than two exist, the one with straight chain is normal, and the least complex structure after this is sometimes called *iso*. An *iso* compound has a single branch at one end of the chain; the rest of the chain is unbranched. An example is seen in 2-methylpentane below. Ambiguity is always avoided by the use of the systems of naming which have just been explained. The isomers of hexane are given below to illustrate what has been said on this subject.

#### Isomeric Hexanes.

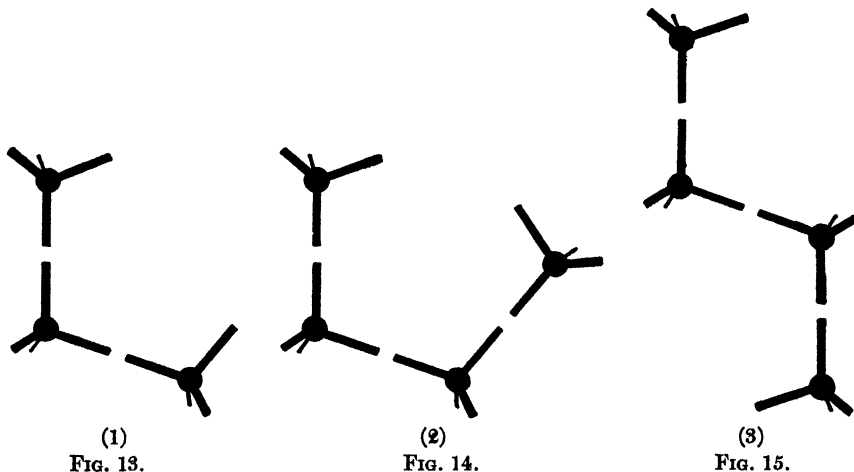




The carbon atoms enclosed by brackets are the nuclei used in naming their compounds by the second system explained above.

In a series of isomeric compounds, such as the hexanes shown above, it will generally be found that the isomer with normal structure has the highest boiling point of the series, while the compound with the most branched structure has the lowest boiling point. Inspection of the boiling points of the hexanes will show the variations which exist in this series.

**Nature of Carbon Chains.** In writing formulas it is usually convenient to place the carbon atoms of a chain in a straight line as we have done, but we realize that they are not actually so arranged. The angles of the valence bonds with each other prevent such an arrangement. A three-carbon chain is actually as shown in (1) below, and a four-carbon chain as in (2) or (3), or in any arrangement intermediate between these two.\*



Long chains are thus in a zig-zag arrangement or else arranged as open spirals. It is known that the chains of solid paraffins have the zig-zag arrangement. For liquid and gaseous paraffins the helix arrangement is favored by some chemists, not by all.†

## PETROLEUM

Petroleum or "rock oil" is the chief source of the hydrocarbons which are discussed in this chapter. In its crude state petroleum is a thick oil varying in color from a light brown to black. It is contained in pools in

\* The models are set on a flat surface and viewed from above; the picture is somewhat "idealized."

† Molecular models should be used throughout the classroom discussion of the material of this chapter.

and between layers of porous rocks at various depths underground, and wells to tap these pools range from a few feet to about two miles in depth. A three-mile well is a recent achievement.

The origin of the petroleum in the earth is "explained" by several theories. One has it that the action of water upon metallic carbides under heat and pressure caused the formation of the oil, but although some carbides do react with water to yield hydrocarbons (pages 26, 64) there are several strong objections to this theory. There are more facts to support the theory that petroleum was formed in past ages from the decomposition of plant carbohydrates under heat and pressure. The presence of derivatives of chlorophyll in petroleum is thus explained. Also coal (known to have a carbohydrate origin) is often found in the neighborhood of oil deposits. Some of the compounds found in petroleum contain nitrogen and sulfur which also occur in the proteins of plants.

There is as well a theory that petroleum was formed by the decomposition of fish. In support of this there is offered an experiment in which fish blubber was heated under pressure and paraffins like those in petroleum were produced in good yield.\*

Petroleum is found in many parts of the world, large amounts being obtained in the United States (California, Oklahoma, Arkansas, Kansas, Texas, Pennsylvania, Illinois, Ohio, Colorado) and in Canada, Russia, Mexico, Persia, and other places. In Scotland and in certain regions of the United States, notably in Colorado and Utah, a bituminous shale ("Oil Shale"), is present in large quantity. This, when distilled, yields paraffin oils among other products. There is considerable interest in these shales, as the diminishing supply of petroleum† may necessitate their use at some future time as a source of paraffins. Ozokerite or earth wax is a solid wax-like substance, found in many localities, principally in Galicia. This may be used as a substitute for beeswax after a preliminary purification by the use of sulfuric acid, followed by successive washing with water and alkali.

Petroleum contains, in addition to the paraffin hydrocarbons, many others of diverse series, also benzene hydrocarbons and other substances the nature of which varies with the source of the oil. Petroleum is classed as paraffin-base oils and asphalt-base oils, the former leaving upon distillation a residue of paraffin, while the latter yield a product similar to natural asphalt.

**Refining.** In the refining of petroleum it is subjected to distillation and separated into a number of fractions, each of which contains several members of the paraffin series. The products obtained from the distillation include ligroin or "petroleum ether" (boiling range about 35–80°), gasoline (range

\* For interesting discussion see Ipatieff, *Catalytic Reactions at High Pressures and Temperatures*, Macmillan, 1936, p. 586.

† It is quite possible that petroleum is now being formed in the earth and that the available supply is increasing.

about 50–220°), kerosene and other middle oils, heavy oils, vaseline, paraffin wax, and coke. Further purification is necessary to fit these products for the market. See flow sheet, page 788.

To remove objectionable sulfur compounds from gasoline the crude distillate may be treated with concentrated sulfuric acid. Colored impurities are removed at the same time. If the percentage of sulfur compounds is high, "doctor solution" may be used (see page 115). Final treatment consists in a thorough washing and a redistillation.

In the purification of lubricating oils excess wax is removed by chilling. This precipitates the wax which is then removed by filtration. An alternative treatment is to add something to the oil to prevent crystallization of the wax. The best known of such pour point depressants are Parafflow and Santopour. Both are synthetic products. A treatment of the oil with sulfuric acid may be needed to take out sulfur compounds and other impurities.

It has recently been discovered that objectionable compounds may be removed from lubricating oils more advantageously by solvent extraction than by sulfuric acid treatment. Several solvents have been used in this way including furfural (page 641), "chlorex" (page 129), phenol, cresylic acid, and certain mixtures of liquids. Liquid petrolatum is purified by treatment with strong sulfuric acid, then with alkali. Filtration through charcoal follows.

**Cracking.** The large demand for low-boiling compounds to be blended into gasoline has caused the rapid development of several processes for the intentional cracking of the higher-boiling products. The cracking process consists essentially in the breaking down of large molecules of the higher members of the series to yield smaller molecules, and is accomplished by heating the oil under pressure. Cracking applied to crude oils and heavy oils greatly increases the gasoline yield from petroleum. Furthermore, the cracked gasoline has a higher octane rating than that directly distilled from petroleum because of the presence of olefins (page 54) and an increased percentage of branched-chain compounds. Catalytic methods of cracking produced about 36,000,000 barrels of gasoline (1941) out of a total of about 320,000,000 barrels of cracked gasoline.

Aluminum chloride is used as a catalyst in one of the recent cracking processes. The chemical industry as a whole has benefited by the cheap aluminum chloride developed for use in this process. About 50% of our gasoline is now made by cracking.

**Polymerization.** In the cracking operation mentioned, gases are produced belonging to the olefin series (page 49). These are made into liquid motor fuel by a polymerization process. The process involves heat treatment of olefins and saturated hydrocarbons of low molecular weight at a suitable pressure. Phosphoric acid is used as a catalyst in one process. The gasoline so made has high octane rating. See equation, page 43.

**Natural Gasoline. Bergius Process.** The demand for gasoline has also led to the practice of stripping natural gas of its gasoline content. This is known as natural gasoline or "casinghead gasoline." It is too volatile to be used directly, but is mixed with heavier gasolines in making motor fuel. U. S. production (1941) was about 3 billion gallons.

In the Bergius process powdered coal is heated with hydrogen at high temperature and pressure to form a synthetic petroleum from which satisfactory gasoline may be obtained. The Bergius process is also used with petroleum, giving gasoline and lubricating oils of high quality. Low-temperature tar and creosote oil may be hydrogenated to give yields of gasoline of about 80%; the yield from coal is about 60–70% by weight.

**Antiknock Fuel.** New models of automobiles have used ever higher compression ratios with the object of increasing the power per pound of engine weight. The increased compression causes "knocking" with consequent loss of power. Study of the problem has shown that straight-chain hydrocarbons knock more than branched-chain compounds. Compounds of the ethylene series (Chapter III) are antiknock; these are produced in the cracking operation and give added value to gasolines made in this way.

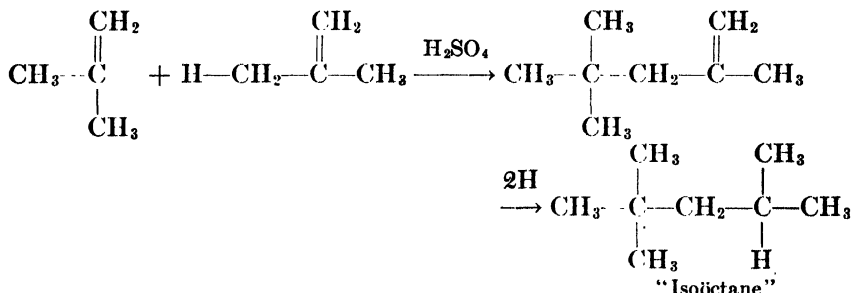
In order to compare automobile fuels with regard to their knocking characteristics the "octane number" is used. The octane number of a gasoline is the number of per cents of 2,2,4-trimethylpentane ("isoöctane") present in a mixture of this compound and *n*-heptane, when the mixture has the same knocking characteristics as the gasoline under examination. On the octane scale *n*-heptane, which knocks badly, has zero rating, and isoöctane is arbitrarily given 100 rating. Octane ratings of typical compounds of several series are given in the table.

Compound	Octane rating	Compound	Octane rating
Ethane.....	100+	Ethene.....	81
<i>n</i> -Heptane.....	0	Propene.....	85
<i>n</i> -Octane.....	-17	Pentene-2.....	80
3-Methylpentane.....	75	Cyclohexane.....	77
2,2-Dimethylbutane.....	96	Benzene.....	100+
2,2,3-Trimethylbutane.....	100+	Toluene.....	100+

Tetraethyllead is now used universally as an antiknock compound; about 60,000,000 pounds were used in 1936 (page 326).

Progress in aviation and in automobile engine design has created a call for fuels with high octane ratings. The methods used to make them cannot be discussed in detail here. They include (1) "hydroforming" of low octane number gasoline (heating in presence of hydrogen and a catalyst); (2) the polymerization of 4-carbon unsaturated compounds to 8-carbon

compounds which add hydrogen to form "isoöctanes." The equation for the preparation of 2,2,4-trimethylpentane is:



(3) The addition of alkanes to alkenes to produce hydrocarbons of high octane rating is noted on page 56. (4) "Isomerization" refers to a change of chain structure. Butane is converted to isobutane when heated with aluminum chloride; *n*-pentane (octane rating 64) isomerizes to isopentane (octane rating 91). Heat treatment of a gasoline to cause isomerization is known as "reforming." For further discussion of the preparation of special motor fuels, see the references of page 47.

PETROLEUM STATISTICS  
Production (in 1000 barrels)

	1939	1940	1941
World.....	2,085,444	2,141,946	2,226,836
United States.....	1,264,962	1,353,214	1,404,182
California.....	224,354	223,881	230,263
Oklahoma.....	159,913	156,164	154,759
Texas.....	483,528	493,209	507,584

Active wells in United States at close of 1937, 351,206; 1940, 389,010.

#### DEUTERIUM COMPOUNDS

Another type of substitution possible to organic compounds which was unknown but a few years ago is that of light hydrogen by heavy hydrogen (deuterium). This is effected in some compounds with ionizable hydrogen by reaction of the compound with heavy water (D<sub>2</sub>O). In other cases D is introduced by the use of heavy hydrogen (D<sub>2</sub>) or its derivatives, with and without the use of catalysts.

The introduction of D atoms into compounds is very important from the biological standpoint. The oxidation of such compounds gives water of higher density than that formed by H compounds.\* This allows one to trace molecules in the organism and see what becomes of them. One can in a sense tag or label the molecules in which such substitution has taken place, since their oxidation gives water containing a certain amount of heavy water. A large number of organic compounds has already been made in which part or all of the hydrogen has been exchanged for deuterium. The concept of isomerism must be broadened to include these compounds. Those which have biological applications must be examined to see the effect

\* See page 411.



produced by the heavy hydrogen. It will be seen that the problems introduced by the discovery of heavy hydrogen will occupy organic chemists for many years.

Deuterioethane ( $C_2D_6$ ) has been made by reaction of  $C_2H_6$  with pure  $D_2$  using a nickel catalyst and a temperature of  $138^\circ$  for several hours. Methane exchanges H for D when heated at  $138^\circ$  or a higher temperature (with nickel catalyst) with  $D_2$ ,  $CD_4$ , or  $D_2O$ . In this

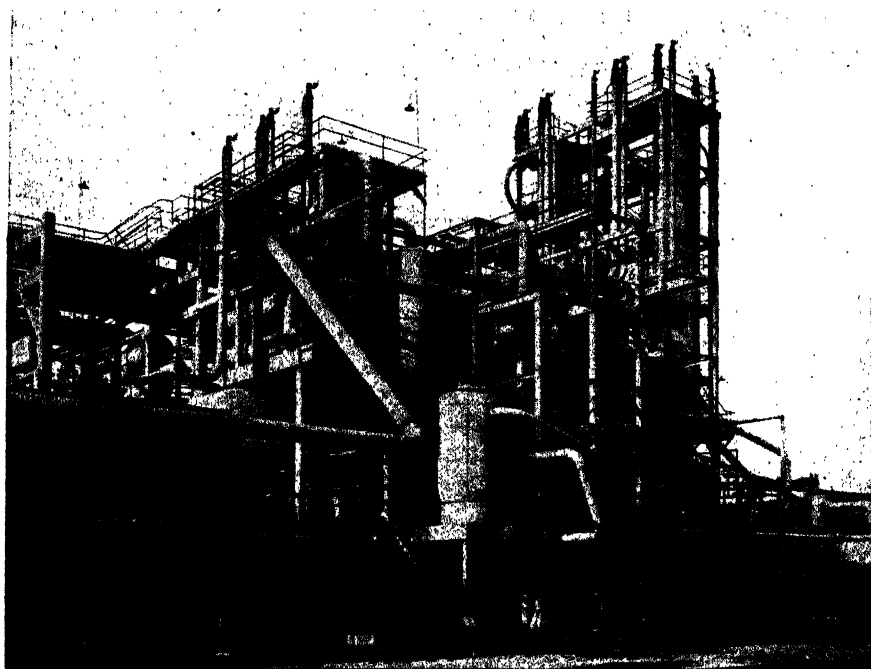


Fig. 16.—Gas absorption plant for recovery of highly volatile light gasoline blending stocks from refinery gases. (Courtesy of Standard Oil Company of Indiana.)

way the compounds  $CH_3D$ ,  $CH_2D_2$ ,  $CHD_3$ , and  $CD_4$  are formed. For the properties of  $D_2$  and  $D_2O$  see page 411.

#### DETECTION OF SATURATED HYDROCARBONS

The saturated hydrocarbons are insoluble in water and in cold, concentrated sulfuric acid. When treated with cold, fuming sulfuric acid, there is some darkening, but solution does not occur. Cold, fuming nitric acid is also without effect. Bromine (carbon tetrachloride solution) reacts slowly, liberating hydrogen bromide. A dilute solution of potassium permanganate does not change color when shaken with a saturated hydrocarbon.

#### REVIEW OUTLINE

In this chapter we have considered the homologous series known as the alkanes. Other homologous series will be taken up in following chapters. After studying a chapter as suggested on page 17 it will be of assistance to

go over it again rapidly with the help of the following outline. This outline covers most of the material in any of the early chapters of this book.

**Occurrence of Compounds.** Do the compounds studied occur in nature? If so, where? How (briefly) are they obtained from their natural source?

**Preparation of Compounds.** What commercial methods are used to make the compounds? If possible, show the methods of synthesis by means of equations. In writing equations it is necessary to show the conditions (temperature, pressure, use of catalysts, etc.) used to promote the reaction when these are known. What methods are used for small-scale laboratory preparation of the compounds? (Equations.)

**Physical Properties.** Consider the physical properties (color, odor, density, melting points, boiling points) of the compounds of the series under consideration.

**Uses.** Are there general uses for which a number of the compounds are adapted? List special uses for individual members of the series.

**Reactions.** Group these under the proper heads: oxidation, substitution, etc. List special reactions separately. Write equations for each type of reaction.

**Nomenclature.** Be sure that the system of naming the compounds is well understood. Write typical formulas with their names.

**Typical Structure.** How can it be shown that the first or second member of the series has the structure represented by the graphic formula?

**Detection.** What physical and chemical traits lead to the detection of compounds of this series in laboratory work?

In making a general review the outline given here may be used first for each chapter. The separate outlines prepared for the chapters as suggested on page 17 should be used next, in order to catch any topics not provided for in the simpler scheme.

### REVIEW QUESTIONS

1. Write equations for two methods of preparation for propane.
2. Write graphic formulas for the following compounds:
  - (a) 2-Methyl-4-ethyl-hexane.
  - (b) 3,3,4-Trimethylhexane.
  - (c) 4-Ethyl-6-methylnonane.
3. Name the following compounds:
  - (a)  $\text{CH}_3\text{CH}(\text{C}_2\text{H}_5)\text{CH}_2\text{CH}(\text{C}_2\text{H}_5)\text{CH}_3$ .
  - (b)  $\text{CH}_3\text{CHCH}_3\text{CH}_2\text{CH}_2\text{C}(\text{CH}_3)_2\text{C}_2\text{H}_5$ .
  - (c)  $(\text{CH}_3)_2\text{CHCH}(\text{CH}_3)\text{CH}(\text{CH}_3)_2$ .
4. Will water extinguish burning hexane? Give reasons for your answer.
5. Write the graphic formulas of compounds which would be formed by the action of sodium upon: (a) Propyl iodide; (b) 2-Iodopropane; (c) 2-Bromobutane.
6. Write the structures for the isomeric pentanes and name each compound.
7. What is meant by the terms: (a) Aliphatic compound; (b) Substitution reaction; (c) Homologous series; (d) Alkyl radical?
8. What theoretical interest attaches to the aliphatic hydrocarbons and to methane in a discussion of organic chemistry?

9. What is the formula of the paraffin whose mol. wt. is: 58? 126? 282?
10. Account for the fact that three pentanes are known.
11. Which of the following formulas might designate members of the paraffin series:  $C_2H_7$ ;  $C_6H_{12}$ ;  $C_3H_6$ ;  $C_4H_9$ ;  $C_{10}H_{22}$ ;  $C_{11}H_{22}$ ? Change the subscripts for H so that all will represent paraffins.
12. Write graphic formulas to show that there are four monochloro derivatives of butane.
13. In the mixture used to get the "octane number" which compound, heptane or trimethylpentane is antiknock?
14. Rock salt is not used as a lubricant, but paraffins are so used. Make a statement regarding the attractive forces existing within these two types of compounds.
15. Suppose two bromine atoms to have been substituted in place of any two hydrogen atoms of normal butane. Write graphic formulas for all of the possible isomeric compounds (molecular formula  $C_4H_6Br_2$ ).
16. If 10 g. of propane were burned in contact with 10 l. of oxygen how much propane (or oxygen) would remain unused? What weight of water would be produced?
17. What chemicals would be used in testing an aliphatic compound (hydrocarbon) to find whether it is a member of the paraffin series? Outline the tests and the result of each of them (assuming that the compound is actually an alkane).
18. When methane is treated with bromine what by-product results? How could one recognize the presence of this by-product?
19. The alkanes are practically odorless compounds, also they are practically tasteless. Can you explain these two facts by reference to any of the physical properties of the alkanes?
20. Which methods of preparation given in this chapter apply only to methane? Which methods of preparation may be used for any member of the series of alkanes?
21. Make a graph on cross-section paper to show the relationship of the boiling points of the normal alkanes (ordinates) to the number of carbon atoms in the compounds (abscissas). On the same paper plot the melting points against the number of carbon atoms. Compare the contours of the two curves obtained. Can you explain why they are so different?
22. List the methods used to make gasoline from petroleum and from coal. List methods which yield antiknock gasoline.
23. Describe briefly the refining of petroleum.
24. Attempts were made to cause *n*-hexane to react with the following reagents (at room temperature). In which cases did reaction take place? (a) Oxygen; (b) Concd. sulfuric acid; (c) Concd. hydrochloric acid; (d) Concd. potassium hydroxide solution; (e) Chlorine; (f) Iodine; (g) Potassium permanganate solution; (h) Sodium metal.
25. If we attempt to make propane through the Wurtz reaction, using sodium, methyl iodide, and ethyl iodide, will any hydrocarbon save propane be formed? Why?
26. The complete combustion of a mole of a certain alkane produced three moles of carbon dioxide. How many carbon atoms does the alkane possess? How many moles of water were produced in the combustion?
- (R)27.\* Calculate the heat of combustion of each of the following alkanes: methane, propane, pentane, octane, decane. Compare the results with the experimental values given in this book (see page 69).

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\* Questions marked (R) are intended for use in a general review. Their solution may require information which is given in later chapters of the book.

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# CHAPTER III

## UNSATURATED HYDROCARBONS

### ETHYLENE SERIES

#### (Olefins, Alkenes)

As we have seen, the hydrocarbons of petroleum are largely alkanes, compounds of formula  $C_nH_{2n+2}$ . An examination of the compounds produced in the cracking of these alkanes shows the presence of hydrocarbons belonging to a different homologous series, of type formula  $C_nH_{2n}$ . These hydrocarbons differ markedly from the alkanes. Quite a number of them had been made and studied long before the refining of petroleum was of importance. They form the ethylene or olefin series, the simplest member of which is  $C_2H_4$ , ethylene.

#### PHYSICAL PROPERTIES OF ETHYLENE COMPOUNDS

In general, the members of the ethylene group resemble the paraffins in their physical properties. The first three members, ethylene,  $C_2H_4$ ,

TABLE 4.—PHYSICAL CONSTANTS OF SOME NORMAL ALKENES

Names, common	Official names	Formulas	M.p., °C.	B.p., °C.	Sp. g., 20°/4°	Ht. of comb., Kg. cal./ mole	Calcu- lated No. of isomers
Ethylene.....	Ethene	$C_2H_4$	-169.4	-103.9	0.570 <sup>-103.9</sup>	337.3	1
Propylene.....	Propene	$CH_2=CHCH_3$	-185.2	-47.6	0.610 <sup>-47</sup>	491.8	1
n-Butylene.....	1-Butene	$CH_2=CHCH_2CH_3$	-139.0	-6.24	0.625 <sup>-6</sup>	649.7	3
n-Amylene.....	1-Pentene	$CH_2=CH(CH_2)_2CH_3$	-138.0	30.1	0.641	806.8	5
n-Hexylene.....	1-Hexene	$CH_2=CH(CH_2)_3CH_3$	-141.0	63.7	0.671	903.9	11
n-Heptylene.....	1-Heptene	$CH_2=CH(CH_2)_4CH_3$	-120.0	92.8	0.697	1120.9	27
n-Octylene.....	1-Octene	$CH_2=CH(CH_2)_5CH_3$	-102.1	121.6	0.715	1277.9	66
n-Nonylene.....	1-Nonene	$CH_2=CH(CH_2)_6CH_3$		145.0	0.732	1434.9	153
n-Decylene.....	1-Decene	$CH_2=CH(CH_2)_7CH_3$	-80.0	172.0	0.742	1591.9	377
n-Hendecylene.....	1-Hendecene	$CH_2=CH(CH_2)_8CH_3$		189	0.763	1748.9	914
n-Dodecylene.....	1-Dodecene	$CH_2=CH(CH_2)_9CH_3$	-31.0	213.0	0.760	1905.9	2,281
n-Tridecylene.....	1-Tridecene	$CH_2=CH(CH_2)_{10}CH_3$	-13.0	192 <sup>10</sup>	0.767	2062.9	5,690
n-Tetradecylene.....	1-Tetradecene	$CH_2=CH(CH_2)_{11}CH_3$	-12.0	114 <sup>3</sup>	0.774	2219.9	14,497
n-Hexadecylene.....	1-Hexadecene	$CH_2=CH(CH_2)_{13}CH_3$	4.06	158 <sup>11.5</sup>	0.783	2533.9	93,650
n-Octadecylene.....	1-Octadecene	$CH_2=CH(CH_2)_{15}CH_3$	18.0	179 <sup>15</sup>	0.788	2847.9	623,338

propylene,  $C_3H_6$ , and the butylenes,  $C_4H_8$ , are gases under ordinary conditions. The next higher members are colorless liquids similar in appearance to liquid paraffins, while the compounds with more than 18 carbon atoms in

the molecule are solids. They do not have so many representatives in nature as have the paraffins; they may however be produced in the destructive distillation of complex natural substances. This explains the presence of ethylene in coal gas. Table 4 gives the formulas, melting points, boiling points, and densities of some representative olefins.

### CHEMICAL PROPERTIES OF ETHYLENE HYDROCARBONS

In their chemical properties ethylene and its congeners differ widely from compounds of the paraffin series. They are much more reactive and they have a wider variety of reactions than do the methane hydrocarbons. For example, ethylene reacts with the halogens. It also enters into combination with the halogen acids, sulfuric acid, hypochlorous acid. Ethylene may be reduced and its oxidation is easily effected. It is obvious that these compounds must have a structure quite different from that of the paraffins.

### STRUCTURE OF ETHYLENE

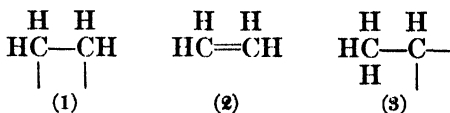
Ethylene readily enters into reaction with chlorine, bromine, or iodine, to form new compounds. With chlorine the reaction is violent, and means must be taken to check it (low temperature and absence of light). Bromine and iodine react less violently in the order stated. In all of these cases no by-product is produced as in the reaction of halogens with methane (page 33), but both atoms of the halogen molecule attach directly to ethylene to form a new compound:



The other reactions mentioned (with halogen acids, sulfuric acid, etc.) consist likewise in addition of the reagent to the ethylene molecule without the formation of a by-product:



These reactions make it seem likely that in ethylene not all the valence of the carbon is being utilized; some is left over, so to speak. The following structures are proposed to show this. They represent the three possible arrangements of two carbons and four hydrogens, allowing for the tetravalency of the carbon atoms.



The plan shown in (3) is ruled out because if such a compound added chlorine both Cl atoms would be attached to one carbon atom. Now the compound

\* Ethylene reacts most readily with hydrogen iodide and least with hydrogen chloride. This order of reactivity is opposite to that of the halogens with the methane hydrocarbons, where chlorine is most reactive and iodine non-reactive.

FRIEDRICH WÖHLER. (1800-1882, German.) A worker in the organic and inorganic fields. The organic student meets him on the first page of the text because of his urea synthesis, and later hears of his work with Liebig on the benzoyl radical. Wöhler and Liebig were life-long friends. See *Am. Chem. J.*, **4**, 289 (1882), *J. Chem. Soc. (London)*, **43**, 258 (1883), *J. Chem. Education*, **5**, 1537 (1928); also this book, pages 3, 269.



*Berichte*, **23**, 833 (1890).



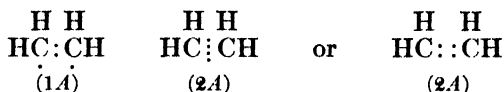
*Berichte*, **23**, 817 (1890).

JUSTUS F. VON LIEBIG. (1803-1873, German.) The founder of agricultural chemistry. A pioneer in chemical education, a devoted and gifted teacher, whose laboratory was for many years the Mecca of chemists from all Europe and beyond. His joint work with Wöhler on benzoyl radical was of great service to the science. Like Bunsen, Liebig invented many pieces of laboratory apparatus which are still in daily use. See *J. Chem. Education*, **4**, 1461 (1927), *ibid.*, **8**, 211, 223 (1931), **13**, 557 (1936), **15**, 553 (1938), **18**, 221 (1941); *J. Chem. Soc. (London)*, **27**, 1204 (1874), **28**, 1065 (1875); also this book, page 262.



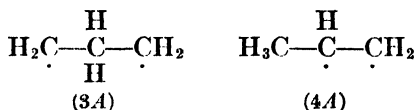
$C_2H_4Cl_2$  indicated in the equation above has been made in other ways, and it has been shown that the two chlorine atoms are not attached to the same carbon atom.

The (partial) electronic formulas for (1) and (2) above are as follows:



It might seem as if either of these would serve equally well, but such is not the case. Formula 1A allows each carbon atom only seven electrons, while formula 2A in which two pairs of electrons are jointly held between carbons, allows a full octet to each carbon.

Also if we accept formula (1A) for ethylene we could write propylene, the next higher member as in (3A). This could add  $Cl_2$  to give 1,3-dichloropropane. Another form of propylene could also exist (formula 4A). This would add  $Cl_2$  to give 1,2-dichloropropane.



Now when compounds of the ethylene series add new elements or groups they always take two at a time and *always on adjacent carbons*. Thus formula 3A becomes impossible and 1A seems highly improbable. Formula 2A is the only structure which accords with the behavior of ethylene and the other olefins. We will use this kind of formula, then, for compounds like ethylene in which only part of the valence of the elements is needed to hold the molecule together. Ordinarily the formula will be written as in (2).

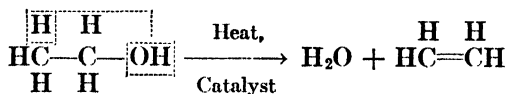
A union like that pictured in (2) is called a **double bond**. Such a compound is said to be **unsaturated**, since all the available valence is not needed to hold the molecule intact, i.e., atoms are held to each other by more than one valence bond. The other members of the ethylene series have also a double bond structure. The reactions which pertain to this grouping are thus common to all of the members of this series.

One is tempted to think of a double bond as "stronger" than a single bond. This conception would be false. The fact is that the double bond is ruptured by a number of reagents which do not affect single bonds in the same molecule. The **double bond functions as a point of attack**, and reactions are initiated which may ultimately split the molecule at this point. This reactivity of the double bond may be due to the fact that neither pair of electrons of the group of four can occupy the preferred position.

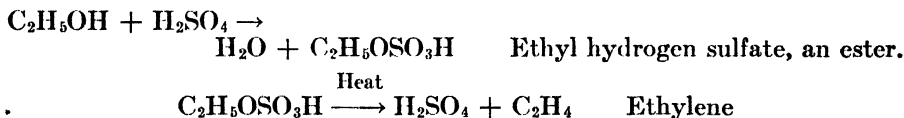
## PREPARATION OF ETHYLENE HYDROCARBONS

There are a number of methods by means of which ethylene may be prepared, the more general of which are as follows:

(1) Dehydration of ethyl alcohol. This may be accomplished by passing the vapor of alcohol over a suitable catalyst (a heated metallic oxide may be used):\*



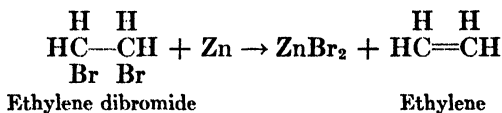
or by the use of sulfuric or phosphoric acids which act as dehydrating agents. When either of these acids is used we have first a reaction of ethyl alcohol with the acid to form a compound called an ester, which next breaks down to regenerate the acid and yield ethylene. The following equations show how these reactions proceed with ethyl alcohol and sulfuric acid:



It will be noted that the sulfuric acid is regenerated in the second phase of this reaction, and may then convert more alcohol into ethylene; this is accordingly known as a "continuous process." In practice, the sulfuric acid is somewhat used up in side-reactions, so that one lot of acid cannot convert unlimited quantities of alcohol into ethylene. Phosphoric acid more nearly fulfills the theoretical stipulations. The student will later find (page 123), that ether may be produced by this same reaction, under slightly different operating conditions.

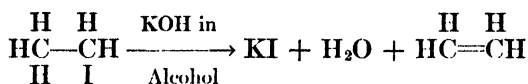
Esters of primary alcohols with benzenesulfonic acid (page 439) give olefins when heated. There is an advantage in this method over that which uses sulfuric acid because no charring takes place.

(2) The action of an active metal on an ethylene dihalide produces ethylene:



(3) An ethyl halide will yield ethylene if heated with a solution of potassium hydroxide in alcohol (alcoholic potash):

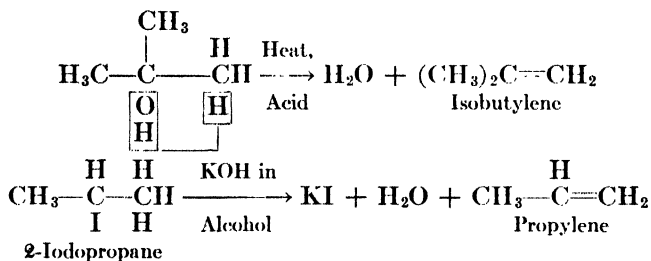
\* See Ipatieff, *Catalytic Reactions at High Pressures and Temperatures*, Macmillan, 1936, p. 62.



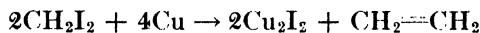
In the absence of water the halogen acid (HI in this example) is removed from the molecule. When water is present, OH substitutes for the halogen atom and an alcohol is produced (page 81).

It will be noted that in each of these examples we have contrived to **remove atoms or groups from adjacent carbon atoms of a chain**. The same principle may be extended for the formation of higher members of the series. The following are examples:

Preparation of isobutylene and of propylene:

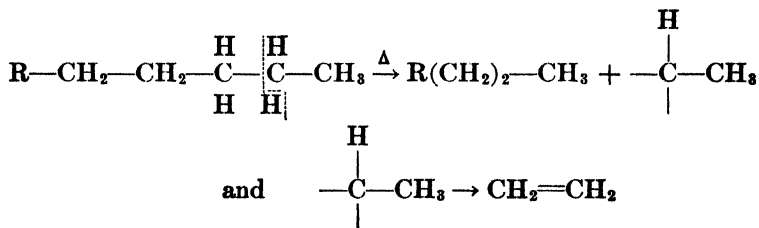


It is noteworthy that methylene,  $\text{CH}_2$ , which apparently should head this series, has never been isolated. Reactions which might be expected to yield methylene give instead ethylene:



The methylene may exist momentarily, but apparently two groups at once join to each other to form ethylene.

In the process of cracking (see page 32) we note the production of hydrocarbons of the ethylene type from saturated hydrocarbons. It is possible to make ethylene from ethane by heating to about  $700^\circ$ . One might typify the production of ethylene from a long-chain saturated compound as follows:



however the reactions which occur are actually very complex. During the cracking process various fragments unite to form larger molecules which may belong to new series; free carbon and hydrogen also appear. It would be quite wrong to picture the cracking operation as a simple change

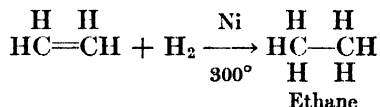
of saturated hydrocarbons to unsaturated compounds and short-chain saturated compounds. In this connection, see references, page 73.

### REACTIONS OF ETHYLENE HYDROCARBONS

The reactions of these compounds are reduction, oxidation, addition, and polymerization; with the paraffins reduction is impossible, oxidation is difficult, and addition does not occur. Thus the hydrocarbons of these two groups though alike in their physical aspects may easily be distinguished by their chemical differences.

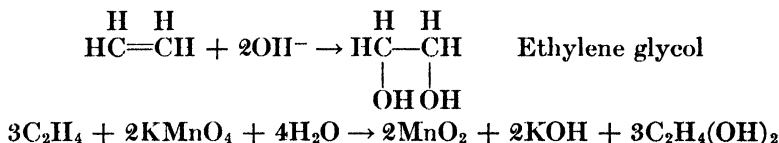
The following equations show examples of the reactions noted above.

(1) *Reduction.* In the presence of hydrogen and a suitable catalyst ethane is formed by the reduction of ethylene:



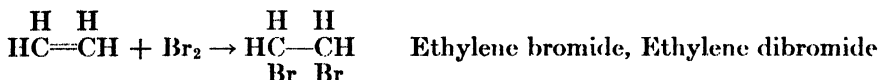
This reaction, known as **hydrogenation**, is characteristic for olefins.

(2) *Oxidation.* Strong oxidizing agents may completely oxidize ethylene to carbon dioxide and water. With mild oxidation in water solution, or in a solution of a base,  $\text{OH}^-$  ions are taken up to form ethylene glycol:

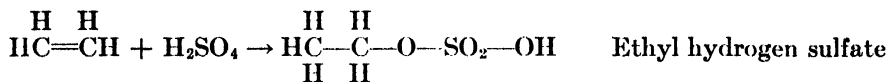
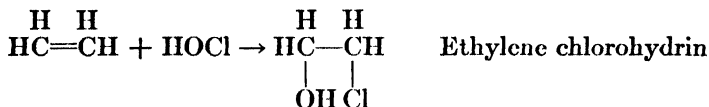
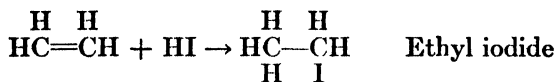


This reaction forms the basis of the Baeyer test for the double bond, in which a dilute solution of potassium permanganate is used. The reduction of the permanganate is shown by fading of the violet color of the solution. Certain other groups also reduce permanganate solution, but if these are known to be absent the positive test indicates a multiple bond. If this oxidation be continued, by the use of a warm concentrated permanganate solution, the molecule usually splits at the site of the double bond, forming two molecules of organic acids. Examples will be shown later.

(3) *Addition.* Many compounds and some elements are added by olefins to form new compounds which are saturated:



Note that here there is no by-product as in the action of a halogen on a saturated hydrocarbon. Here we have *addition*, with the saturated series we have *substitution*. Further examples of the addition reactions of ethylene are seen in the following equations:



When addition occurs between the higher members of the olefin series and polar compounds having unlike positive and negative parts, there is the possibility of the formation of two different compounds, thus:



In this particular instance the reaction takes place almost exclusively according to (1) in the absence of oxidizing agents, thus following Markownikoff's (Markovnikov's) rule (1870) which states that in such additions the more negative part of the added reagent will attach to the carbon bearing the smaller number of hydrogen atoms (or the larger number of alkyl groups).

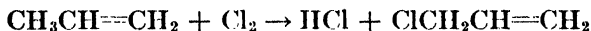
While Markownikoff's rule may be applied in a number of cases, it is not universally satisfactory. Many instances are known in which additions occur in both possible ways, the relative yields of the two addition compounds varying according to the nature of the groups next the double bond, and according to the experimental conditions.

The most important variable is the presence or absence of oxygen or organic peroxide compounds, though strong light also has an effect; temperature and the nature of the solvent may likewise be important. In the presence of peroxides propylene reacts according to equation (2) above.\*

*Addition of paraffins.* It has recently been discovered that paraffin hydrocarbons will add to olefins in the presence of catalysts (sulfuric acid, aluminum chloride). An example is the addition of isobutane to the butenes in the presence of sulfuric acid to yield octanes. In commercial preparation of motor fuel of high octane rating a mixture of butanes and butenes is treated with sulfuric acid. The *n*-butane, which does not react, is separated from the products and either isomerized to isobutane (page 43) or dehydrogenated to yield butenes. The other components of the original butane-butene mixture combine to yield hydrocarbons of the gasoline range. The reactions which occur are complex (see References, page 73).

\* Hydrogen iodide reacts according to equation (1) with propylene, whether peroxides are included or excluded.

(4) *Substitution.* When propylene is chlorinated at 400–600° substitution is the principal reaction:



Allyl chloride (yield 80%+)

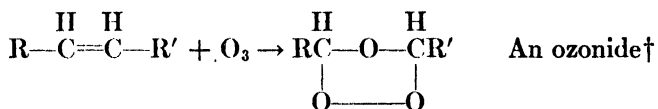
The allyl chloride may be used for the synthesis of glycerol (page 109).

(5) *Polymerization.* Compounds of the olefin series (with the exception of ethylene)\* may undergo a reaction called polymerization, when treated with such reagents as sulfuric acid or zinc chloride. Under such conditions two or more molecules of an olefin unite with each other to form new compounds having two or three or more times the molecular weight of the simple olefin. The reaction of polymerization is more or less common to unsaturated compounds (see page 67). It has great importance in connection with the making of gasoline (page 42), plastics, and synthetic rubber.

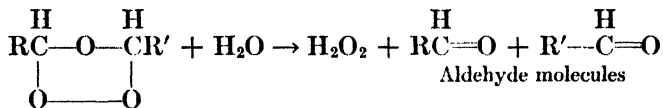
Single molecules are *monomers*; when two molecules unite we have a *dimer*; union of three molecules yields a *trimer*, union of  $n$  molecules a *polymer*. The splitting of such compounds to their originals is *depolymerization*.

Unsaturated compounds in cracked gasoline may in time form gums because of oxidation and polymerization reactions. The formation of such gums, which are detrimental to the use of the fuel is prevented by the use of inhibitors (phenolic compounds, aromatic amines). See page 513.

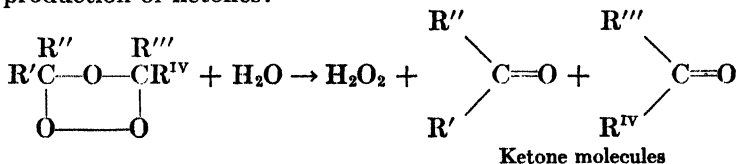
*Reaction with ozone.* Ethylenic compounds add ozone at the double bond to form compounds called ozonides:



An ozonide treated with water splits at the site of the double bond with the creation of hydrogen peroxide and two carbonyl compounds:



The carbonyl compounds have either aldehyde or ketone structure depending upon the presence of hydrogen or alkyl groups at the double bond. In the above example aldehydes are produced. The following equation illustrates production of ketones:



\* In order to polymerize ethylene, a high temperature is required.

† The exact structure of the ozonides is still in doubt.

When an aldehyde is a product of the hydrolysis, its oxidation by hydrogen peroxide is avoided by the use of a reducing agent, such as zinc dust.

This reaction is of great service for the location of a double bond in a chain. Examination of the compounds produced by the scission to determine the number of carbon atoms in each is a necessary preliminary. The oxidation by permanganate previously mentioned is used in like fashion to fix structures of unsaturated compounds.

The olefins react much more readily than the saturated hydrocarbons. This may be attributed to a state of "strain" in the double bonds (page 610), which makes rupture of one of these bonds much easier than the breaking of a single bond in a saturated hydrocarbon. In the presence of certain reagents the double bond opens readily, allowing absorption of the reagent, and producing a derivative of a saturated hydrocarbon.

### NOMENCLATURE. ISOMERISM

Ethylene and its homologs form a series with the type formula  $C_nH_{2n}$ . The members are called *alkenes*, also *olefins*; the latter name arises from the fact that ethylene was at one time called olefiant gas (because it forms an oily liquid when acted upon by chlorine).

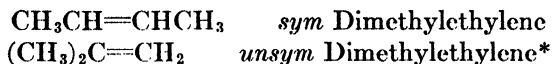
Names of compounds of the olefin series are derived naturally from the names of the paraffins of like carbon content, by substituting the name ending "ene" or "ylene" for "ane."

Thus:

$C_2H_6$ , Ethane.....	$C_2H_4$ , Ethene or Ethylene
$C_3H_8$ , Propane.....	$C_3H_6$ , Propene or Propylene
	$C_4H_8$ , Butene or Butylene
	$C_5H_{10}$ , Pentene or Amylene, etc.

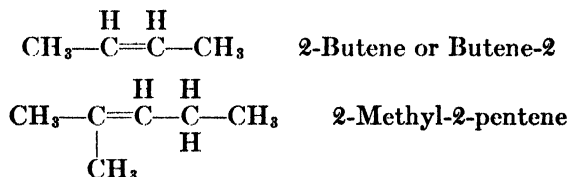
The compounds of this series may likewise be named as derivatives of ethylene.

Thus:



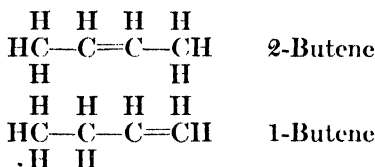
or the position of the double bond may be indicated by using a number to show at which atom the double bond originates. The formula is arranged to make this number as small as possible.

Example:



\* *sym* = symmetrical; *unsym* = unsymmetrical.

**Isomerism of Unsaturated Hydrocarbons.** Opportunities for isomerism among the unsaturated compounds are greater than for the saturated series, since not only the size and disposition of the groups in the compound may be altered, but the position of the double bonds is also of prime importance. Thus, for example, there is but one normal butane but there are two normal butenes, each having a straight chain and differing only in the position of the double bond:



Another kind of isomerism is possible, due to the fact that when two carbons are joined by a double bond a rigid structure results. This can

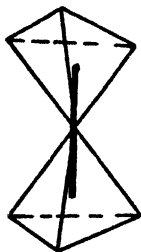


FIG. 17.

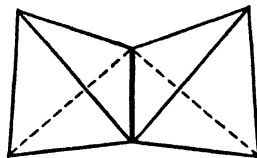


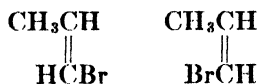
FIG. 18.

best be shown by models (made conveniently from corks), such as are illustrated in diagram in the accompanying figures. When two carbon atoms are joined by a single bond (Fig. 17), free rotation is possible around the axis common to both carbon atoms.

When, however, we have two bonds between the carbons (Fig. 18), the possibility of free rotation is lost.

Thus for a compound like  $\begin{array}{c} \text{H} \quad \text{H} \quad \text{H} \\ \text{HC} - \text{C} = \text{C} \\ \text{H} \qquad \text{Br} \end{array}$ , there are two forms possible, differing

in their space relationships and not superposable\* (Figs. 19 and 20).



\* These diagrams are slightly distorted to better show the relationships between the carbon atoms.



This form of isomerism is termed *geometrical isomerism*, a form of stereo-isomerism. Further examples will be found on later pages.

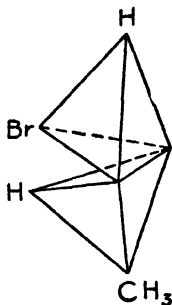


FIG. 19.

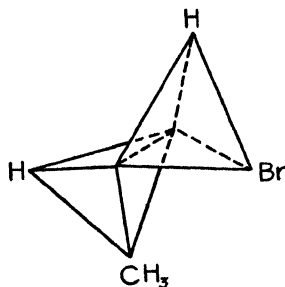


FIG. 20.

### USES OF ETHYLENE HYDROCARBONS

Ethylene has been found to be an effective anesthetic for general anesthesia. Propylene is an even more powerful anesthetic but is not now in use. In California, citrus fruits are colored by the use of ethylene. The gas is used to hasten the ripening of bananas and other fruits, and certain derivatives (particularly the chlorohydrin, page 56) have similarly been used to shorten the dormancy period of potatoes. In coal gas the luminosity of the flame is due in part to the presence of this hydrocarbon. About 75 commercial chemicals are now made from ethylene; Whitmore (1937) listed 11 made from propylene. Other olefins also find their chief use as source materials and as components of gasoline.

### DIOLEFINS. DIENES

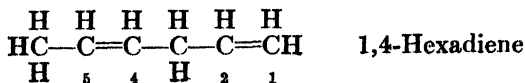
#### (Alkadienes)

The diolefins are a series of compounds which resemble the olefins in their possession of double bond structures, but have two such groupings in the molecule as indicated by the group name. The example given below illustrates a typical compound of the diolefin series, and also shows the scheme of nomenclature, which is as follows: the suffix "diene" is added to the "stem" of the name of the corresponding alkane. Thus we have:

Butadiene.....	four carbons
Hexadiene.....	six carbons

The position of the double bonds is shown in the same manner as was indicated for the olefins, i.e., by the use of the numbers of the carbons at which the double bonds originate. The numbers are made as small as possible by proper choice of the #1 carbon.

Example:



CHEMICAL RELATIONSHIPS OF ETHYLENE

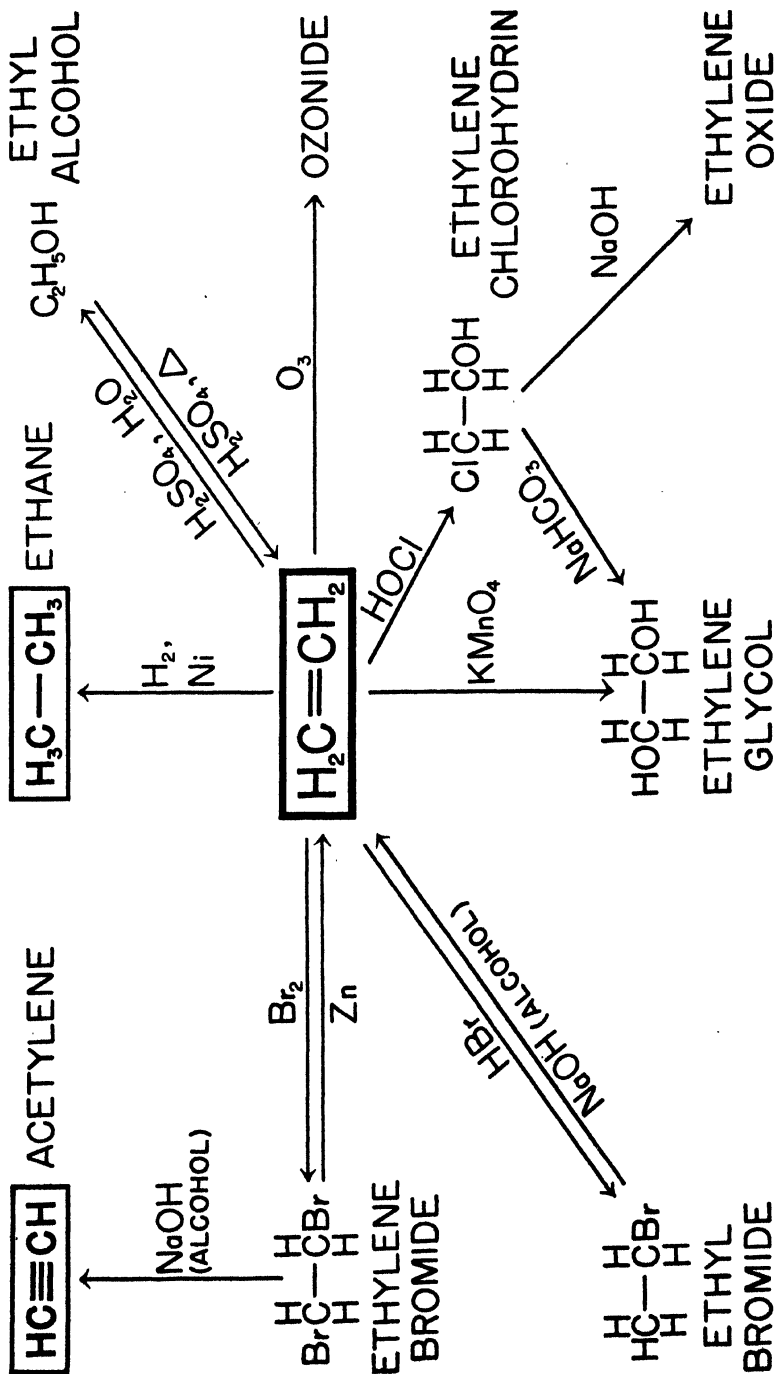
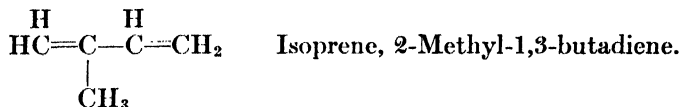


CHART I\*

\* Note remarks on page 69 relative to the preparation of charts.

Diolfins are prepared by methods like those which have been shown for the olefins. The importance of the diolefins does not merit an extended discussion; on the other hand, considerable interest attaches to several individual members. One of these is called isoprene:

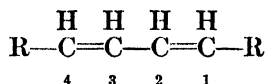


This substance is produced by the destructive distillation of India rubber; the latter has also been made from isoprene. In view of the tremendous importance of rubber in modern life, and especially for a nation at war,\* this synthesis has received much study. It is more practical at present to make synthetic rubber from butadiene than from isoprene. Production plans as first announced for 1943-4 were to make butadiene as follows (expressed in terms of tons of finished synthetic rubber):

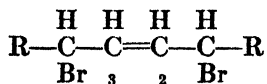
(a) From alcohol.....	242,000
(b) From butane.....	66,500
(c) From butylene.....	283,000
(d) From cracking of oils.....	20,000
(e) From combination of (c) and (d).....	93,500

Butylene glycol was (1942) being made from fermentation of starch. It is possible to obtain butadiene in good yield from the glycol, therefore this method may later be used on the large scale. In addition there are several industrial methods for the production of butadiene from ethyl alcohol.

The reactions of the diolefins are similar to those of ethylene and its homologs. There is, however, an important exception. When double bonds are found next to each other as shown in the following formula:



absorption often takes place in a peculiar way. When such a compound absorbs one molecule of bromine, it can take up the two atoms at positions 1-2 or 3-4† as might be expected from a study of the reactions of ethylene. Also it may take the two atoms at 1 and 4, at the same time forming a new double bond at 2-3. The compound which results in this case is shown below.

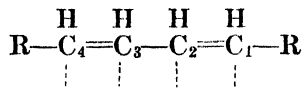


A system having double bonds arranged next to each other like this is said to have **conjugated double bonds**. The manner of its reaction is

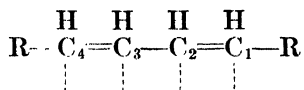
\* A tank may use a ton of rubber; there is about half a ton in the landing wheels of a large airship; a battleship uses about seventy-five tons.

† The conjugated system, for convenience, is numbered independently.

explained by Thiele as follows. He supposes that not all of the valence of the carbon is used to hold atoms together when double bonds are present in a compound (page 50). The unused residual valence which he calls *partial valence*, is represented in the following formula by the dotted lines:



The partial valences of carbons 2 and 3 will tend to satisfy each other, thus:



therefore only the partial valences of carbons 1 and 4 are free to absorb reagents. After absorption at 1 and 4, the partial valences of carbons 2 and 3 are free, and the ethylene bond is shared by these carbons.

There are other explanations of the 1-4 addition reactions of conjugated double bonds, which will be found in advanced texts. Diolefins are more reactive than are monolefins and they polymerize much more readily. This polymerization, which has considerable importance, as already indicated, will be discussed later.

### ACETYLENE SERIES

#### (Alkynes)

We have so far studied two systems of hydrocarbons, the methane series, composed of substances which are called saturated, and the ethylene series, which, with the diolefins, contain unsaturated compounds. We now come to another series of even greater unsaturation than the olefins. Its first member, and the only one which we shall study, is Acetylene,  $\text{C}_2\text{H}_2$ .

This substance is formed by the decomposition at red heat of many organic substances, or during destructive distillation of compounds. Coal gas contains about one-tenth per cent of acetylene formed in this way.

In their physical properties the members of the acetylene series are not unlike the hydrocarbons already studied. Acetylene is a gas, which as ordinarily prepared has a garlic-like odor due to impurities, but when pure is not unpleasant. One volume of water will dissolve about one volume of acetylene, while acetone will dissolve 25 times its volume under atmospheric pressure, and very much larger amounts when the pressure is increased.

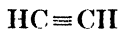
### CHEMICAL PROPERTIES OF ACETYLENE

Acetylene, being a highly unsaturated compound, possesses certain phases of reactivity which distinguish it from ethylene, while in some respects it behaves in a similar manner. Hydrogen bromide and hydrogen iodide are taken up by acetylene, also hydrogen if a catalyst is used. Acety-

lene does not react so readily with the halogens as does ethylene. No action occurs with chlorine in the absence of light, and in diffuse daylight the reaction is slow.\* Under pressure acetylene is explosive and dangerous. The most striking difference between acetylene and ethylene is the ability of the former to form salts with various metal ions, such as silver or copper. Certain of these salts are highly explosive.

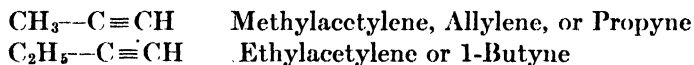
#### STRUCTURE OF ACETYLENE. NOMENCLATURE

In accordance with its molecular formula,  $C_2H_2$ , acetylene is assigned the following structural formula:



which contains a triple bond. The reasoning which supports this formula is based on the addition reactions of this compound and upon its manner of preparation, both of which points will be taken up later.

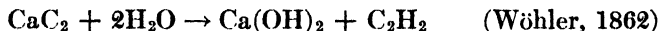
The type formula of this series is  $C_nH_{2n-2}$ ; the compounds of the series are isomeric with members of the series of diolefins. Many of these compounds are known. It will, however, be unnecessary to study them in detail. A few examples are listed here in order to show the nomenclature in this series.



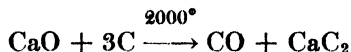
These compounds are named either as derivatives of acetylene or as members of the *alkyne* series (by adding "yne" to the stem of the corresponding methane hydrocarbon term). The ending is pronounced as "ine" in wine.

#### PREPARATION OF ACETYLENE

(1) The common method of preparation involves the reaction between calcium carbide and water:



Calcium carbide is made in the electric furnace from lime and coke:

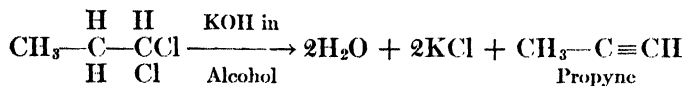


therefore the above represents a synthesis from the elements. The carbides of sodium, potassium, strontium, barium, and of still other metals also give acetylene when they are treated with water. Small amounts of acetylene may also be formed if an arc is produced between carbon poles in an atmosphere of hydrogen. A better yield is obtained by the cracking of methane, diluted with hydrogen, at temperatures over  $1000^\circ$ .

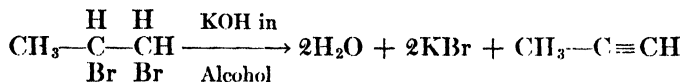
(2) Acetylene hydrocarbons may, like the olefins, be produced from halogen products of the hydrocarbons.

\* See remarks on page 66 on reaction of impure acetylene and chlorine.

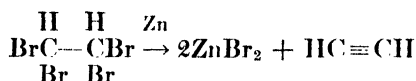
(a) By action of potassium hydroxide (in alcohol) on a hydrocarbon dihalide. The halogen atoms may be on the same carbon:



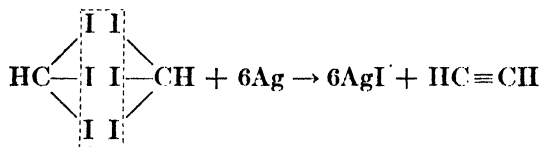
or on adjoining carbon atoms:



(b) Action of an active metal on a hydrocarbon tetrahalide produces an acetylene hydrocarbon:



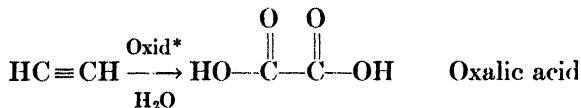
The reactions illustrated above furnish evidence for the presence of a triple bond in acetylene hydrocarbons, which is strengthened by the following synthesis of acetylene from iodoform and silver powder:



### REACTIONS OF ACETYLENE

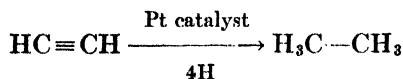
The reactions of acetylene and its homologs are oxidation, reduction, addition, substitution, and polymerization. In other words these compounds share the reactions of the olefins and the alkanes.

(1) *Oxidation.* The oxidation of acetylene may yield oxalic acid:



In this synthesis, mercuric nitrate is used as a catalyst, and nitric acid as oxidizing agent. Carbon dioxide is formed by more severe oxidation.

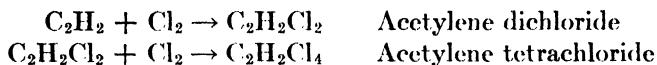
(2) *Reduction.* Reduction of acetylene, in presence of hydrogen, leads to the production of ethene; finally of ethane:



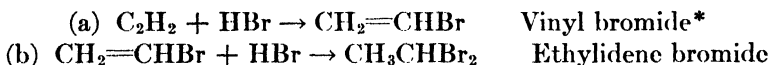
\* Oxidations will be indicated in this text by the abbreviation "Oxid," placed over the sign of reaction. Accessory reagents are often placed about the arrow, in order that the reacting substances and products may stand out more clearly on the page. The above equation may be translated as follows: "Oxalic acid may be produced by oxidation of acetylene in an aqueous medium." Equations of this kind are usually not balanced.

(3) The *addition reactions* of acetylene resemble those already presented for ethylene, but since the compound is less saturated, or in other words has triple instead of double bonds, it can absorb two atoms for one that ethylene would absorb in a given case. It must not be implied, however, that the greater degree of unsaturation makes acetylene more reactive than ethylene; actually it reacts with bromine more slowly than does ethylene.

Impure acetylene reacts violently with chlorine, to form hydrogen chloride and carbon; or to give  $C_2H_2Cl_4$  if a catalyst is used ( $SbCl_5$ ). The purified gas absorbs chlorine slowly in diffused light:



Hydrogen bromide reacts as shown in the following equation:

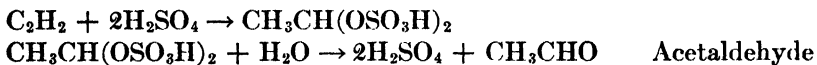


Step (b) may be reversed in the presence of peroxides (see discussion, page 56):



Hydrogen iodide reacts similarly. Vinyl chloride, which is prepared by passing acetylene into concentrated hydrochloric acid containing ammonium chloride and cuprous chloride, is used in the preparation of plastics (page 506).

Water is added by acetylene if the gas is treated with mercuric sulfate in dilute sulfuric acid solution, thus forming acetaldehyde in excellent yield. The oxidation of the latter is a means of preparing acetic acid, which is a basic chemical for many important processes.



(4) *Substitution reactions.* If acetylene is treated with an ammoniacal solution of cuprous chloride, a chocolate-colored precipitate is obtained, having the formula  $Cu_2C_2 \cdot H_2O$ :

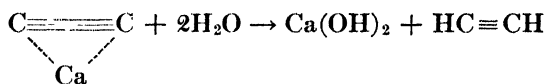


Metal salts of acetylene, such as the above, are called *acetylides*. The silver salt,  $Ag_2C_2 \cdot H_2O$ , may be formed by a reaction similar to that shown above. The sodium and potassium salts are made by passing the gas over the heated metal. These salts of acetylene are apt to be explosive when dry, especially salts of the heavy metals, and accidental explosions of acetylene are often laid to the formation of such salts.†

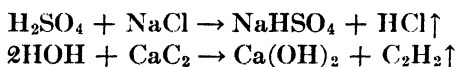
\* The radical  $CH_2=CH-$  is called vinyl. See list of radicals, page 805.

† The sodium and potassium salts are not explosive.

The reaction pictured above shows that hydrogen which is joined to a carbon bearing a triple bond is replaceable by metals (note that  $\text{H}-\text{C}\equiv\text{N}$  is an acid. See page 285). Compounds like the following,  $\text{H}_3\text{C}-\text{C}\equiv\text{C}-\text{CH}_3$ , in which there is no hydrogen atom joined to the triply-bound carbon, do not form metal derivatives. We have seen that acetylene is commonly formed from one of its salts, calcium carbide,  $\text{CaC}_2$ , by the action of water:



When we consider calcium carbide (or acetylide) as a salt of acetylene, the reaction between water and this salt becomes analogous to that between any acid and the salt of a weaker or more volatile acid. The following examples will illustrate this point:



In such cases the weaker, or more volatile acid is displaced by the stronger acid. In its possession of salt-forming powers, and in the reaction of calcium carbide with water, acetylene behaves like a weak acid.

(5) *Polymerization.* When acetylene is heated to a high temperature it polymerizes, forming a great variety of compounds with different catalysts and different temperatures. It is possible to make benzene in this way in good yield, also other aromatic compounds. By a change of conditions aliphatic compounds both saturated and unsaturated are formed.

In the presence of cuprous and ammonium chlorides, acetylene adds itself to give vinylacetylene,  $\text{CH}_2=\text{CH}-\text{C}\equiv\text{CH}$ , divinylacetylene, and still higher polymers. The first named compound is used to make chloroprene for Neoprene rubber (see page 626).

**Deuterium Exchange.** Acetylene, treated with heavy water, exchanges H for D to form  $\text{C}_2\text{D}_2$ .

TABLE 5.—ALKYNES

Common name	Official name and formula	M.p., °C.	B.p., °C.	Sp. g., 20°/4°	Ht. of comb.
Acetylene.....	Ethyne, $\text{HC}\equiv\text{CH}$	— 81.0	— 83.6	0.615 <sup>-80,3</sup>	310.0
Allylene.....	Propyne, $\text{HC}\equiv\text{CCH}_3$	— 102.7	— 23.23	0.671 <sup>-24</sup>	473.0
Ethylacetylene.....	1-Butyne, $\text{HC}\equiv\text{CC}_2\text{H}_5$	— 122.5	8.6	0.678 <sup>0</sup>	626.4
Dimethylacetylene.....	2-Butyne, $\text{CH}_3\text{C}\equiv\text{CCH}_3$	— 32.2	27.1	0.687 <sup>27</sup>	
Propylacetylene.....	1-Pentyne, $\text{HC}\equiv\text{CC}_3\text{H}_7$	— 98.0	39.7	0.695	782.0
Ethylmethylacetylene..	2-Pentyne, $\text{CH}_3\text{C}\equiv\text{CC}_2\text{H}_5$	— 101.0	55.9	0.712	
Butylacetylene.....	1-Hexyne, $\text{HC}\equiv\text{CC}_4\text{H}_9$	— 132.0	71.2	0.715	940.5
Amylacetylene.....	1-Heptyne, $\text{HC}\equiv\text{CC}_6\text{H}_{11}$	— 81.0	99.15	0.734	1091.2
Butylmethylacetylene..	2-Heptyne, $\text{CH}_3\text{C}\equiv\text{CC}_4\text{H}_9$	.....	109	0.745 <sup>25</sup>	
Ethylpropylacetylene..	3-Heptyne, $\text{C}_2\text{H}_5\text{C}\equiv\text{CC}_3\text{H}_7$	.....	106.0	0.765 <sup>19</sup>	
Hexylacetylene.....	1-Octyne, $\text{HC}\equiv\text{CC}_6\text{H}_{13}$	— 79.5	126.17	0.746	1243.5



## USES OF ACETYLENE

When acetylene burns in air a very hot flame is produced, and the free carbon which is liberated at the same time is heated to high incandescence. Accordingly, acetylene finds wide employment as an illuminant in situations where gas or electricity is found too expensive; also for special use in buoys and lighthouses. The gas may be liquefied at  $1^{\circ}$  by a pressure of 48 atmospheres, but the liquid acetylene is very explosive. Explosions also take place when the gas itself is stored under pressure, possibly due to the formation of metallic salts as already suggested. The present practice is to dissolve it under pressure in acetone, which is carried within the gas tank on some porous medium.

Acetylene burned with oxygen in a special type of burner gives an intensely hot flame, which is used for welding purposes and for cutting metal. The use of acetylene for the production of acetaldehyde and acetic acid has already been mentioned. A number of important halogen compounds are made from acetylene. Quite recently the preparation of vinylacetylene for Neoprene has assumed great importance. Acetylene has been used as an anesthetic but it is not as satisfactory as ethylene, and, inhaled in larger amounts, it appears to be dangerously toxic.

**Heating Values.** The hydrocarbons of the three classes studied so far are valuable for the heat produced when they are burned. Some average values for heat production are:

Fuel oil.....	150,000 B.T.U. per gallon
Natural gas.....	1,400 B.T.U. per cu. ft.
Propane (bottled).....	21,600 B.T.U. per pound
Kerosene.....	135,000 B.T.U. per gallon
Anthracite coal.....	14,000 B.T.U. per pound
Coal gas.....	600 B.T.U. per cu. ft.
Gasoline.....	124,500 B.T.U. per gallon
Wood.....	5,000 B.T.U. per pound

**Heat Values for Individual Compounds.** A comparison of the heats of combustion of alkanes, alkenes, and alkynes shows that the molecular structures of the compounds are directly connected with the energy to be obtained by combustion.

Example	Heat of combustion		Difference
	(2)	(3)	(4)
Ethane.....	372.8 Kg. cal.	(393)	-20.2 Kg. cal.
Ethylene.....	337.3	(325.6)	+11.7
Acetylene.....	310.0	(257.2)	+52.8

In the table above, column (2) shows the heat of combustion in kilogram calories per gram-molecular weight, while column (3) gives in parentheses the heat obtained by burning an equal weight of carbon and hydrogen. In the case of ethane more heat is obtained from the free elements; this shows that when these elements combine to form ethane heat is lost in

the amount shown in column (4). Ethylene, however, has a higher heat of combustion than the same weight of free carbon and hydrogen, which shows that in the formation of the compound heat (11.7 Kg. cal. per mole) must be added. For the formation of a mole of acetylene 52.8 Kg. cal. of energy must be added. Ethylene and acetylene are seen to be stored with additional energy. In the graphic formula this is signified by the multiple bond, which is always taken to represent a seat of potential energy.

**Calculation of Heat of Combustion.** The Kharasch method for computing the heats of combustion of individual compounds has been developed from a consideration of the number of electrons which shift their positions during a complete oxidation. For saturated hydrocarbons the heat value in Kg. cal. per gram-molecular weight is obtained by counting the electrons of all C—C and C—H bonds which are broken in the oxidation, and multiplying the sum by 26.05.

**Example 1.** Methane burns to  $\text{CO}_2$  and  $\text{H}_2\text{O}$  with the breaking of four bonds. Thus eight electrons are shifted, and the heat of combustion is  $8 \times 26.05 = 208.4$  Kg. cal. The value quoted in the literature is 212.8 Kg. cal.

**Example 2.** Ethane. Calculated value, 364.7 Kg. cal. Literature value, 372.8 Kg. cal. The values calculated by this method agree well with those obtained by experimental work.\*

**Atomic Spacing in Hydrocarbons.** Of late years physical methods have been perfected which have made it possible to determine the distance between atoms in organic compounds. The distance between carbon atoms depends upon the nature of the bond. Thus we have:

Bond	Distance
C—C.....	$1.54 \text{ \AA} = 1.54 \times 10^{-8} \text{ cm.}$
C=C.....	1.32
C≡C.....	1.20

The C—H distance is 1.09 Å. If we bear in mind that atomic kernels repel each other, the close spacing in acetylene helps to explain its greater store of energy.

### GENETIC RELATIONS OF COMPOUNDS

Our consideration of the hydrocarbons up to this point has concerned itself with their properties, nomenclature, structures, uses, methods of preparation, and reactions. The latter have been presented in such a way as to set the different series apart as much as possible.

It now becomes desirable to take up the close relations of alkanes, alkenes, and alkynes. One of the most important features in a study of organic chemistry is a knowledge of such relations. The organic chemist as a transformer of materials must know how to pass from one kind of compound to another; since all the organic compounds contain nearly the same elements, the relationship between series is very intimate, and brings up considerations which are not needed in a study of inorganic chemistry.

A simple method of illustrating at the same time all the important reactions of a substance, and also its relations to compounds of other series, is shown in the charts of genetic relations of ethylene and acetylene, on pages 61, 70. The student is urged to prepare similar charts for other members of these series, say for propylene and propyne, writing the equations for the reactions below the chart.† Work of this kind will form an excellent

\* For further data see Gilman, *Organic Chemistry*, Wiley, 1943, page 1798.

† The equations should indicate the conditions needed to carry out the necessary reactions (ordinarily omitted from the charts in this book).



review of the material, and will make much lighter the task of learning the reactions and relations of compounds.\* Other methods of review were suggested on pages 17 and 44.

## SUMMARY OF NOMENCLATURE

	Methane (Paraffins) (Alkanes) $C_nH_{2n+2}$	Ethylene (Olefins) (Alkenes) $C_nH_{2n}$	Acetylene (Alkynes) $C_nH_{2n-2}$
<b>Number in series</b>			
<i>one</i>	Methane, $CH_4$	Methylene, $CH_2=$ (Does not exist)	Methyne, $CH\equiv$ (Does not exist)
<i>two</i>	Ethane, $C_2H_6$	Ethylene, $C_2H_4$ (Ethene)	Acetylene, $C_2H_2$ (Ethyne)
<i>three</i>	Propane, $C_3H_8$	(Propene), $C_3H_6$ Propylene	Propyne, $C_3H_4$ (Allylene or Methyl- acetylene)
<i>four</i>	Butane, $C_4H_{10}$	Butene, $C_4H_8$	Butyne, $C_4H_6$
<i>five</i>	Pentane, $C_5H_{12}$	Pentene, $C_5H_{10}$	Pentyne, $C_5H_8$
	Main reaction is substitution.	Main reaction is addition, i.e., the compounds of these series tend to become saturated.	
<b>Radicals—Monovalent</b>	$CH_3$ , Methyl $C_2H_5$ , Ethyl $C_3H_7$ , Propyl $H_3C-\overset{\overset{H}{ }}{C}-CH_3$ , Isopropyl, etc.	<b>Divalent</b> $=CH_2$ , Methylene $H_2C-\overset{\overset{ }{ }}{CH_2}$ , Ethylene $H_3C-\overset{\overset{H}{ }}{C}-\overset{\overset{ }{ }}{CH_2}$ , Propylene, etc.	
Type $C_nH_{2n+1}$ .	Add "yl" to stem of name of corresponding saturated hydrocarbon.	Type $C_nH_{2n}$ .	Add "ylene" to stem of name of saturated hydrocarbon. All of these divalent radicals save methylene exist also as compounds of the olefin series.

**Detection of Unsaturated Hydrocarbons.** Unsaturated hydrocarbons dissolve in cold, concentrated sulfuric acid; this reagent may cause polymerization, which is indicated by carbonization or the separation of resins. The behavior of the unsaturated hydrocarbons with bromine and with potassium permanganate, and other data will be found on previous pages of this chapter and on page 771.

## REVIEW QUESTIONS

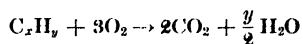
1. Show structural formulas of the compounds formed by the action of bromine upon the several butenes.
2. Name and illustrate the isomeric pentenes.
3. State the evidence which supports a double-bond structure for ethylene, propylene, etc.
4. What chemical reaction shows that the double bond is a "point of attack" in a carbon chain?

\* These charts do not show all of the possibilities; they are offered as models for the work to be done by the student. It would be a mistake to memorize the charts to avoid doing the work suggested.

5. In what sense is the production of ethylene from ethyl alcohol and sulfuric acid a "continuous process"?
6. 3,4-Dibromohexane is treated with zinc; the reaction-product is then treated with hydrogen iodide. What is formed? Give name and structural formula of the new compound.
7. Show the products formed by the action upon propylene of:
  - (a) Sulfuric acid,
  - (b) Chlorine,
  - (c) Hypochlorous acid,
  - (d) Hydrogen iodide,
  - (e) Hydrogen (with catalyst),
  - (f) Dilute solution of potassium permanganate.
8. (a) Show the reaction-product formed by the addition of bromine to 1,5-heptadiene.  
(b) Show what product is formed when one mole of bromine adds to 1,3-heptadiene.
9. Write the type formulas for all types of hydrocarbons studied up to this point.
10. What type of alkyne is able to form a metallic salt?
11. Show two possible structures for 2-pentene and explain the type of isomerism involved.
12. Do all metallic carbides yield acetylene when treated with water?
13. What is the chemical relationship between (a) Acetylene and oxalic acid; (b) Acetylene and acetic acid?
14. By what chemical reaction may acetylene be distinguished from ethylene? Write equation for the reaction.
15. What hydrocarbons would be produced from the following reactions: (a) 2,2-Dibromopropane and alcoholic KOH solution; (b) 1,2-Dibromopropane and alcoholic KOH; (c) Diiodomethane and zinc?
16. What objections are there to the use of a double bond to show unsaturation?
17. How might one separate a mixture of ethane, ethylene, and acetylene so as to preserve the ethane?
18. A sample of pure hydrocarbon when treated with a solution of bromine in  $\text{CCl}_4$  quickly decolorized it. There was no evidence of  $\text{HBr}$ . What was signified by this test?
19. Calculate the heat of combustion of each of the following compounds: *n*-pentane, *n*-hexane, 2-methylpentane.
20. A substance is found to contain C and H only. It burns with a sooty flame and quickly reduces  $\text{KMnO}_4$  solution. Ammoniacal cuprous chloride solution is unaffected by it. To what series may the compound belong?
21. How many grams of bromine could be added by 0.25 mole of propylene?
22. A gram-molecular weight of ethylene was put into reaction with bromine. The product weighed 100 grams. What per cent yield was obtained? How many grams of zinc would be needed to make ethylene from the product?
23. How might methylacetylene, present as an impurity in a sample of dimethylacetylene, be removed? Describe the process and sketch any special apparatus which might be required.
24. A mixture of ethylene and ethane is contaminated with a small amount of acetylene. Devise and describe a method for determining quickly the approximate percentage of acetylene in this mixture.
25. What is a "conjugated diene"? State and illustrate the Thiele theory as applied to dienes.
- (R)26.\* An olefin was treated with ozone and subsequently with water. Final products from this treatment were acetaldehyde and propionaldehyde. What was the original olefin?
- (R)27.\* A certain olefin, treated as outlined in question 26(R) gave acetone and acetaldehyde as final products. What was the original olefin?
- (R)28.\* An olefin, oxidized by hot permanganate solution, gave only propanoic acid as a final product. What was the original olefin?

\* See footnote, page 46.  $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$

29. When ethylene is exploded with oxygen it is found that one volume of ethylene requires three volumes of oxygen and yields two volumes of carbon dioxide. Use these facts and the equation:



- to prove the molecular formula of ethylene. What law of chemistry underlies this proof?
30. A sample of gas is either propane, propene, or propyne. Describe those tests which would identify the compound.
31. A liquid hydrocarbon is treated with bromine in  $CCl_4$  solution. How could you tell if a reaction had taken place? How could you tell the kind of reaction which had occurred?
32. A solution weighing 10 g. and containing 2-pentene was treated with bromine. The solvent was of a type which does not react with bromine. It was found that 14 g. of bromine had reacted with the pentene. What was the percentage of pentene in the solution which was tested?
33. Suppose that a sample of bromine-water was shaken for some time with 1-pentene. What would you expect to happen? What indication would there be of a change?
34. If a spark occurred within a container of pure ethylene would the material explode?
35. Three corked bottles are given to a student taking a "practical examination." He is told that one contains methane, one air, one ethylene. What is the simplest procedure for identifying each substance?
36. A student is given a colorless liquid. It is said to be either water or some aliphatic hydrocarbon. How does he proceed with the identification?

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## HALOGEN DERIVATIVES OF HYDROCARBONS

We have seen that it is easy to treat hydrocarbons in such a way as to replace hydrogen atoms by halogen. Compounds formed in this way are purely synthetic. None of them are found in nature, yet they are among the most useful of the aliphatic compounds. Before beginning their study it will be well to review a few general considerations. It will be remembered that the plan of study depends upon the fact that all the organic compounds may be grouped in homologous series, each of such series containing compounds more or less alike in chemical properties and differing from each other by the increment  $\text{CH}_2$  or a multiple of this group.

Any individual aliphatic compound consists of a carbon skeleton, a certain number of hydrogen atoms and (unless the compound is a hydrocarbon) certain atoms or groups of atoms which have replaced hydrogen. The reactions of the compound as a whole are a summation of the reactions of the hydrocarbon skeleton and of the foreign atoms. Our study properly began with a consideration of different kinds of carbon skeletons, straight, branched, saturated, and unsaturated. The simplest compounds formed from the hydrocarbons are their halogen derivatives. These will have the types of reaction belonging to the carbon skeleton (already studied in previous chapters) and in addition will have new reactions which are associated with the halogen.

A reactive atom or group of atoms replacing a hydrogen in an organic compound is known as a **functional group** or **function**. When two "functions," in this case hydrocarbon and halogen, are associated in a molecule, it frequently happens that the mode of reaction of each is altered by the presence of the other. Ordinarily, however, such changes are not serious and do not interfere with the systematic study of homologous series that has been proposed.\*

## TYPES OF HALOGEN COMPOUNDS

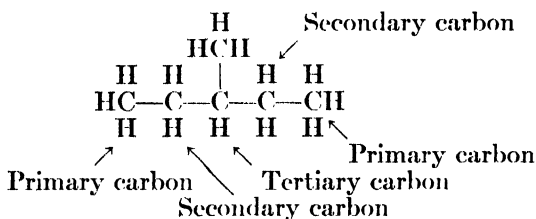
Halogen compounds may be grouped according to the number of halogen atoms per molecule into mono- and polyhalogen compounds. The monohalogen compounds are commonly called *alkyl halides*. We use X to indicate a halogen atom; thus RX is the symbol for any alkyl halide.

**Monohalogen Derivatives.** The monohalogen derivatives of the hydrocarbons are conveniently classified as primary, secondary, or tertiary

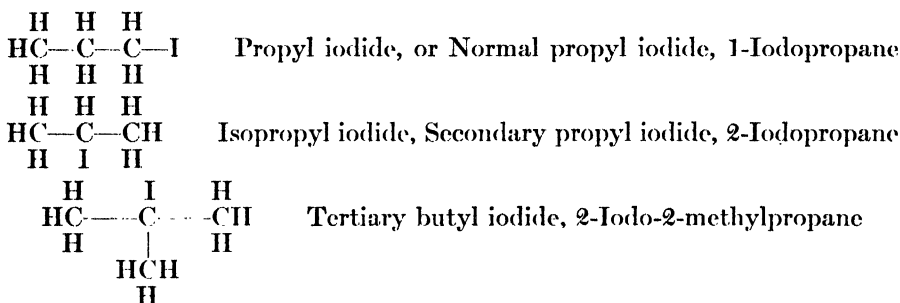
\* Some chemists do not regard a hydrocarbon chain as a function.



according to whether their halogen is attached to primary, secondary, or tertiary carbon atoms. For a definition of these terms see the example below, also page 32.



The application of this nomenclature to the alkyl halides is shown in the following illustrations:



The above examples sufficiently illustrate the naming of simple compounds; the more complex structures are named in accordance with the rules given on page 36.

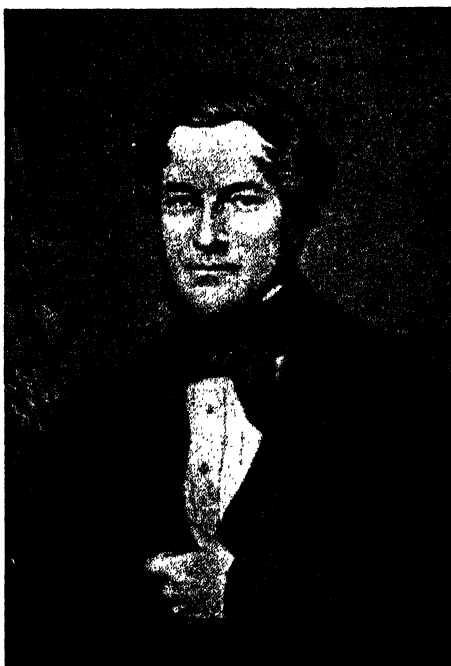
### PHYSICAL PROPERTIES

The alkyl halides of low carbon content have a peculiar, rather sweetish odor, and a sweet taste. The higher members have a less pronounced odor and taste. As a class, they are insoluble in water and in cold, concentrated sulfuric acid; soluble in alcohol, ether, and the common organic solvents. Gases, liquids, and solids are found in this series.\* As will be noted in Table 6, the boiling points of these compounds are considerably higher than those of the hydrocarbons from which they are derived, due to the great increase in molecular weight when a halogen atom is substituted for a hydrogen. The compounds are colorless but some, especially iodides, become colored on standing because of decomposition.

The specific gravities of the fluorides and chlorides lie below that of water, while the bromides and iodides have specific gravities greater than 1. With a given halogen, the specific gravity of the compounds decreases as the

\* That is, at room temperature.

ROBERT W. E. VON BUNSEN. (1811-1899, German.) Prolific worker in analytical chemistry. His work with cacodyl and its compounds, which was of the highest importance for the development of organic chemistry, was done in his early years. The organic laboratory uses many pieces of apparatus which he developed. See *Am. Chem. J.*, **22**, 411 (1899), *J. Chem. Soc. (London)*, **77**, 513 (1900), *J. Chem. Education*, **4**, 431 (1927), *ibid.*, **18**, 253 (1941); also this book page 322.



Fisher Scientific Company.



CHARLES A. WURTZ. (1817-1884, French.) Known as a research chemist, but also for his writings and editorial work with *Annales de Chimie*. He worked with aliphatic amines, halogen compounds (Wurtz reaction), glycols, lactic acid; he made ethylene oxide, choline, alcohols by reduction of aldehydes. See *J. Chem. Soc. (London)*, **47**, 328 (1885), *J. Chem. Education*, **11**, 337 (1934), *ibid.*, **15**, 101 (1938); also this book, page 27.

length of the hydrocarbon chain increases, while for a given number of carbons, the specific gravity rises as we pass from fluoride to iodide.

TABLE 6.—PHYSICAL CONSTANTS OF MONOHALOGEN COMPOUNDS

Name		M.p., °C.	B.p., °C.	Sp. gr., 20°/4°
Common	Official			
Methyl fluoride.....	Fluoromethane	.....	—78.2	
Methyl chloride.....	Chloromethane	—97	—24	0.920 <sup>18°</sup>
Methyl bromide.....	Bromomethane	—93.0	4.5	1.732 <sup>0°</sup>
Methyl iodide.....	Iodomethane	—64.4	42.4	2.279
Ethyl fluoride.....	Fluoroethane	.....	—32.0	1.70*
Ethyl chloride.....	Chloroethane	—139	12.5	0.910
Ethyl bromide.....	Bromoethane	—117.8	38.4	1.431
Ethyl iodide.....	Iodoethane	—105	72.4	1.933
<i>n</i> -Propyl fluoride.....	1-Fluoropropane	.....	—3.0	
<i>n</i> -Propyl chloride.....	1-Chloropropane	—122.8	46.4	0.859
Isopropyl chloride.....	2-Chloropropane	—117	36.5	0.860
<i>n</i> -Propyl bromide.....	1-Bromopropane	—110	70.8	1.353
Isopropyl bromide.....	2-Bromopropane	—89.0	60	1.310
<i>n</i> -Propyl iodide.....	1-Iodopropane	—98.8	102.5	1.743
Isopropyl iodide.....	2-Iodopropane	—90	89.5	1.703
<i>n</i> -Butyl chloride.....	1-Chlorobutane	—123.1	77.9	0.887
<i>n</i> -Butyl bromide.....	1-Bromobutane	—112.4	101.6	1.279
<i>n</i> -Butyl iodide.....	1-Iodobutane	—103.5	129.9	1.617
<i>n</i> -Amyl fluoride.....	1-Fluoropentane	.....	62.8	0.788
<i>n</i> -Amyl chloride.....	1-Chloropentane	.....	105.8	0.878
<i>n</i> -Amyl bromide.....	1-Bromopentane	.....	128.7 <sup>739</sup>	1.218
<i>n</i> -Amyl iodide.....	1-Iodopentane	.....	155.4 <sup>739</sup>	1.510
<i>n</i> -Hexyl chloride.....	1-Chlorohexane	.....	132.9	0.876
<i>n</i> -Hexyl bromide.....	1-Bromohexane	.....	156.0	1.173
<i>n</i> -Hexyl iodide.....	1-Iodohexane	.....	180.0	1.439
<i>n</i> -Heptyl fluoride.....	1-Fluoroheptane	—73.0	119.2	0.804
<i>n</i> -Heptyl chloride.....	1-Chloroheptane	.....	159.5	0.881 <sup>16°</sup>
<i>n</i> -Heptyl bromide.....	1-Bromoheptane	.....	178.5	1.133 <sup>16°</sup>
<i>n</i> -Heptyl iodide.....	1-Iodoheptane	.....	203.8	1.401
<i>n</i> -Octyl fluoride.....	1-Fluorooctane	.....	142.5	0.804
<i>n</i> -Octyl chloride.....	1-Chlorooctane	.....	183	0.892 <sup>0°</sup>
<i>n</i> -Octyl bromide.....	1-Bromooctane	.....	202	1.118 <sup>16°</sup>
<i>n</i> -Octyl iodide.....	1-Iodooctane	—45.9	225.5	1.337 <sup>15°</sup>

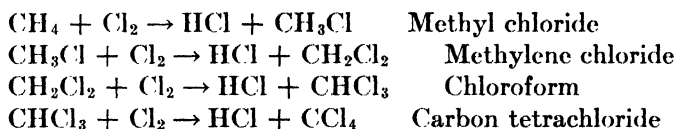
\* Referred to air.

### PREPARATION OF MONOHALOGEN DERIVATIVES

We will first consider the methods of preparation of the primary alkyl halides. These may be made by:

(1) Reaction of a saturated hydrocarbon and a free halogen (page 33). However, in general, this is not a practical method, because more than one

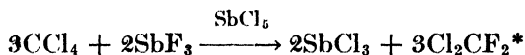
hydrogen atom may be substituted and a mixture of products formed, as illustrated in the following equations:



Another disadvantage of this method is that the reactions are highly exothermic and may become explosive. This reaction has received much study because of its attractive possibilities and the inherent problems will doubtless be solved in due time (see Reference 13, page 92). Methyl chloride is being made commercially by this method. Also a mixture of monochloropentanes, made by chlorination of pentanes from natural gas, is employed for production of amyl alcohols on a large scale. For an indirect method of chlorination see Reference 16, page 92.

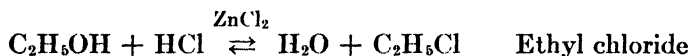
Bromine acts as shown above, but not so readily as does chlorine, while iodine does not take part in such a reaction with the saturated hydrocarbons. Fluorine reacts readily, usually with explosive violence. However it is possible to substitute fluorine atom for another halogen by the use of certain salts.

\* Example. Preparation of dichlorodifluoromethane (yield > 85%):



This compound under the name of Freon is used as a refrigerant. It is practically non-toxic and is non-inflammable.

(2) A convenient and practical method for alkyl halide preparation involves the reaction of a halogen acid with the corresponding alcohol.†



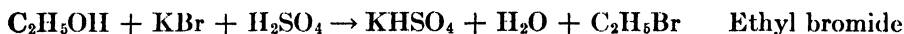
The reaction is reversible; therefore a water-removing substance is employed to obtain the maximum yield of alkyl halide (in accordance with the law of mass action). Sulfuric acid may be so used when making primary halides, but when secondary and tertiary alcohols are employed the acid is apt to form olefins (see page 103). In the case of the iodides and bromides the yield may be increased by employing a large excess of aqueous HI or HBr. Zinc chloride is an effective catalyst for preparation of the chlorides by this method; even in the presence of water a good yield of halide may

\* The example is a polyhalogen compound because no monofluoro compound is of importance at present.

† By corresponding alcohol is meant one with the same number of carbon atoms as the desired halide, and belonging to the same hydrocarbon series, in other words one with an identical carbon skeleton.

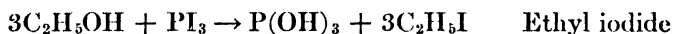
be obtained. In making methyl chloride or ethyl chloride gaseous HCl may be used.

(2a) The necessary halogen acid for this reaction may be prepared within the reaction flask as indicated in the following equation:



This method is inferior to (2) for the preparation of halides higher than  $\text{C}_3$  (due to lower yield).

(3) Iodides may be made from alcohols and excess hydriodic acid, but more conveniently from alcohols and the phosphorus halide.



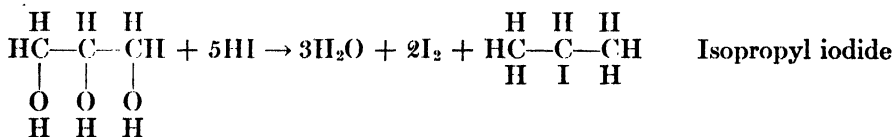
Note that a secondary alcohol would yield a secondary alkyl halide in this reaction. The phosphorus halide is prepared in the reaction flask by adding the correct amount of a mixture of red and yellow phosphorus to the alcohol, then adding the iodine. Phosphorus pentachloride or thionyl chloride may also be used to make halides from alcohols.

(4) Alkyl halides are also formed by addition of a halogen acid to an ethylenic hydrocarbon:



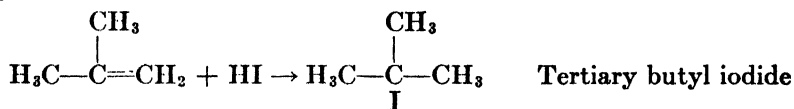
This method is less convenient for laboratory use than those which start with an alcohol. It is well suited to the commercial production of ethyl chloride.

**Secondary and Tertiary monohalogen derivatives** may be prepared by the use of methods 2, 3, and 4 shown above for the primary halides. (Note the exception in 2.) Special methods also are used; for instance, isopropyl iodide may be made in good yield, as shown in the following equation, from glycerol and excess of HI:



**Tertiary Alkyl Halides** may be obtained by addition of a halogen acid to an unsaturated hydrocarbon;\* however method (2) above is more practical.

Example:



It is interesting to consider how many different isomeric compounds might be formed by the introduction of one halogen atom into a long-chain

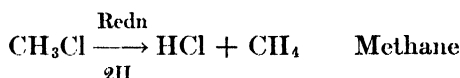
\* The halogen atom attaches to the carbon bearing the smaller number of hydrogens (see page 56).

hydrocarbon. If we monohalogenated all of the isomers of formula  $C_{20}H_{42}$  it would be theoretically possible to produce 5,622,109 compounds. Presumably only a fraction of this number would be produced in an actual experiment of the sort described.

### REACTIONS OF MONOHALOGEN DERIVATIVES

The reactions of the alkyl halides include reduction and "double decomposition," together with several special reactions of new types. Examples of these different reactions are illustrated in the equations which follow.

(1) *Reduction in the presence of hydrogen ion; a saturated hydrocarbon is formed (see page 27):*



(2) *Reaction with an active metal.* (a) Wurtz reaction, see page 27. The student will note that this is a reduction reaction, the metallic sodium acting as a reducing agent:

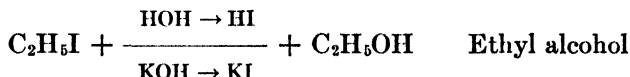


The mechanism of this reaction will be taken up later. It is far from simple, as illustrated by the fact that the reaction gives other products than the "doubled" hydrocarbon. The reaction is unsuited for preparation of hydrocarbons with an odd number of carbons. Reaction of a mixture of  $\text{CH}_3\text{I}$ ,  $\text{C}_2\text{H}_5\text{I}$ , and sodium, to make propane, gives also some  $\text{C}_2\text{H}_6$  and  $\text{C}_4\text{H}_{10}$ .

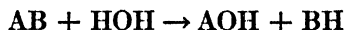
(b) Grignard reaction, see page 83.

(3) *Reactions of exchange or "double decomposition."*

(a) Reaction with water or an aqueous solution of a base (hydrolysis). By this reaction an alkyl halide is transformed to the corresponding alcohol:

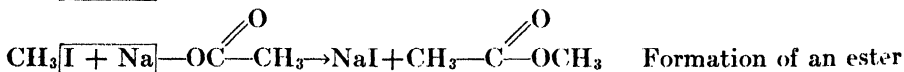
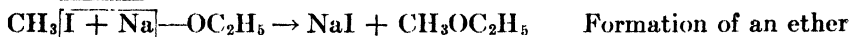
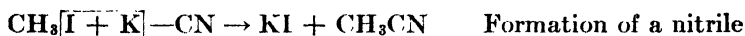


The reaction of hydrolysis has very great importance in organic chemistry and biochemistry. It has two phases: (1) the rupture of the reacting molecule and (2) the linking of the  $\text{H}^+$  and  $\text{OH}^-$  ions of water to the fragments:



In many cases the reaction is reversible (see method (2) page 79). The action of water or alkali upon secondary and tertiary halides produces olefins; primary halides also yield olefins when treated with alcoholic alkali solution. In other words mixtures of compounds are formed in these reactions rather than single compounds. If hydrolysis is the desired reaction the conditions which favor olefin formation must be avoided.

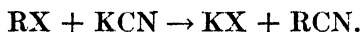
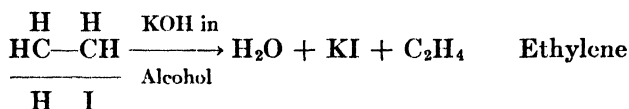
## (b) Reactions with salts.



The above examples of exchange illustrate a type of reaction which is quite general for the alkyl halides, making them very valuable synthetic agents. These reactions will be studied in more detail in later chapters. Note that in these exchanges the incoming group takes the same position that was occupied by the outgoing group or atom. With very few exceptions this is the rule in the exchange reactions of organic compounds.

The equations shown above are the kind commonly used in texts and journals to illustrate the reactions of organic chemistry, and it should be understood that they are purely formal. That is, they are not in any sense explanatory. They show the important chemicals used and often give the conditions necessary for the reactions, but do not show the mechanism of the reactions. This material can be handled more profitably at a later time when more facts have been learned. Also these formal equations are not taken as guides for laboratory work. Before carrying out any of these reactions one would consult directions in a laboratory manual for the necessary details.\*

The equations shown here are for the preparation of specific compounds. To indicate that a reaction is shared by a number of the compounds of a series one uses a **general equation** such as the following:

(4) *Reaction with a base* (in alcohol solution).

We have seen that aqueous alkali will convert an alkyl halide to an alcohol by simple exchange of  $\text{OH}^-$  ion for halogen. When, however, we use an alcoholic solution of base, thus diminishing the hydroxyl concentration, the elements of halogen acid are withdrawn from the halide, producing an ethylene hydrocarbon.

This loss of halogen acid may be caused by simple heating with or without catalysts, or it often occurs while carrying out reaction (2a), page 80, especially with tertiary and secondary halides. In heating a halo-

\* Very often equations of this kind are not completely balanced.

gen compound we sometimes note a shift of the halogen, evidently to a more stable position. Thus *n*-propyl bromide becomes isopropyl bromide. We may suppose that the compound first lost HBr to form an olefin, which again added the HBr in the opposite arrangement:



(5) *Reaction with ammonia and amines.* Ammonia and amines (these are derivatives of ammonia) add alkyl halides forming ammonium salts (see page 303 for equation).

(6) *Reaction with magnesium.* When an alkyl halide is brought into reaction with metallic magnesium in dry ether, the metal acts as a reducing agent and at the same time unites with the organic residue to form a special type of substance known in general as an "organometallic" compound.



Compounds such as the above, made from magnesium and alkyl halides are called **Grignard reagents** after the chemist who discovered their usefulness. They take part in a large number of exceedingly important chemical transformations (see Chapter XXIX).

(7) *Reaction with halogen.* Di-, tri-, and polyhalogen compounds are formed. All possible isomers result, the relative amounts depending upon the conditions imposed. In general the ease of replacement of hydrogen of saturated hydrocarbons is: tertiary > secondary > primary, but at high temperature the replacement is purely random.

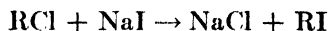
## REACTIVITY OF ALKYL HALIDES

The reactions which we have shown in the preceding section indicate the wide range of usefulness of alkyl halides in synthetic work. These compounds do not, however, show equal reactivity in following these transformations. In general, it may be said that the iodides are more reactive than the bromides, and they in their turn react with greater facility than the chlorides. Compounds with short carbon chains are more reactive than those with many carbons; thus we find methyl and ethyl iodides are preferred "alkylating agents" for laboratory work. In industrial work the less expensive chlorides are used. By using pressure vessels (autoclaves) it is possible to employ fairly high temperatures and in this way the reactivity of the chlorides may be enhanced.

Primary halides are generally more reactive than the isomeric secondary and tertiary compounds; however a comparison of reactivity, to be fair, should consider each reaction separately. The tertiary compounds do not form esters and ethers as illustrated on page 82; instead olefins are apt to be formed. Since iodides are more reactive than chlorides, it is sometimes



desirable to change halogens before a reaction. This may be done by the use of sodium iodide (and otherwise):



### POLYHALOGEN DERIVATIVES OF HYDROCARBONS

Hydrocarbon derivatives in which more than one halogen atom have been introduced form a large and interesting group. They are conveniently divided into the following classes:

- (1) Compounds with a single carbon atom.
- (2) Compounds with more than one carbon atom.

TABLE 7.—PHYSICAL CONSTANTS OF POLYHALOGEN COMPOUNDS, ETC.

Common name	Official name	M.p., °C.	B.p., °C.	Sp. g., 20°/4°
Methylene chloride.....	Dichloromethane	-96.7	40-1	1.336
Methylene bromide.....	Dibromomethane	-52.8	98.5	2.408 <sup>25</sup>
Methylene iodide.....	Diiodomethane	+5.2	180 dec.	3.325
Fluoroform.....	Trifluoromethane	.....	20(40 atmos.)	2.53
Chloroform.....	Trichloromethane	-63.5	61.2	1.489
Bromoform.....	Tribromomethane	+8-9	150.5	2.890
Iodoform.....	Triiodomethane	119.0	sub.	4.10
Carbon tetrafluoride.....	Tetrafluoromethane	-80.2	-12.8	.....
Carbon tetrachloride.....	Tetrachloromethane	-22.6	+76.8	1.595
Carbon tetrabromide.....	Tetrabromomethane	(α)48.4	189.5	3.42
Carbon tetraiodide.....	Tetraiodomethane	dec.	sub. in vac.	4.32
Ethylene chloride.....	1,2-Dichloroethane	-35.3	83.7	1.258 <sup>17</sup>
Ethylene bromide.....	1,2-Dibromoethane	+10.0	131.5	2.180
Ethylene iodide.....	1,2-Diiodoethane	81-2	dec.	2.132 <sup>10</sup>
Ethylidene chloride.....	1,1-Dichloroethane	-96.7	57.3	1.175
Ethylidene bromide.....	1,1-Dibromoethane	.....	108-110	2.055
Ethylidene iodide.....	1,1-Diiodoethane	.....	178	2.84 <sup>0</sup>
Vinyl chloride.....	Chloroethylene	.....	-12	.....
Vinyl bromide.....	Bromoethylene	-138	+15.8	1.529 <sup>4</sup>
Vinyl iodide.....	Iodoethylene	.....	56.0	2.08 <sup>0</sup>
Acetylene dichloride ( <i>cis</i> ).....	.....	-50.0	48.4	1.250 <sup>16</sup>
Acetylene dichloride ( <i>trans</i> ).....	.....	-80.5	60.3	1.291 <sup>16</sup>
Acetylene dibromide ( <i>cis</i> ).....	.....	-53	110.2	2.285 <sup>17</sup> 6'

The second class is still further divided into subgroups in which:

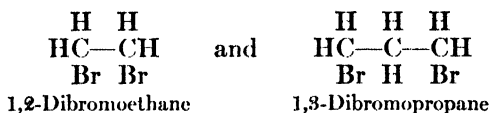
- (a) Halogen is concentrated upon a single carbon atom.

Example:



- (b) Halogen is joined to separate carbons.

Examples:

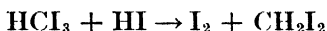


The boiling points and specific gravities of some representative compounds of these series are shown in Table 7.

#### COMPOUNDS WITH ONE CARBON ATOM

The more important of these compounds will be briefly considered.

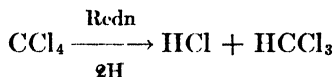
**Methylene iodide, Diiodomethane,  $\text{CH}_2\text{I}_2$ .** The high molecular weight of this compound, caused by its large percentage of halogen, gives it a specific gravity greater than that of any liquid save mercury. Accordingly, it may be used to separate substances, notably minerals, which have different specific gravities. When mixed in varying proportions with benzene, whose specific gravity is 0.878, a liquid of any specific gravity lying between these two figures (3.325 and 0.878) may be obtained. This serves to separate substances whose densities lie on either side of that of the chosen mixture. Freshly mined coal may be cleared of slate and shale in this way. Methylene iodide may be prepared by the action of hydriodic acid upon iodoform:



or by reduction of iodoform with sodium arsenite in alkaline solution.

**Methylene chloride** is used as a refrigerant in air conditioning equipment.

**Chloroform,  $\text{HCCl}_3$ ,** is made on the large scale by the action of iron and dilute acid upon carbon tetrachloride:

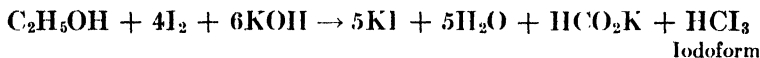


It can be made by action of chlorine upon alcohol, and is often made in the laboratory from acetone and bleaching powder. Both of these reactions will receive further consideration.

Chloroform is a heavy liquid with a peculiar sweet odor and a sweetish taste.\* It is still used to some extent as an anesthetic, although ether is less harmful to the system. Chloroform has, however, the advantage of being non-inflammable. It is an excellent solvent for fat, and also dissolves rubber. Among the reactions of chloroform, we are particularly concerned with its decomposition by light and air, as this gives rise to phosgene,  $\text{COCl}_2$ , along with chlorine and hydrogen chloride (see page 260). The presence of these substances is very undesirable if the chloroform is to be employed as an anesthetic. Decomposition is largely prevented by keeping chloroform in well-stoppered brown glass bottles, with the addition of about 1% of ethyl alcohol.

\* Compounds with several chlorine atoms are generally sweet. Chloroform is 40 times as sweet as cane sugar. Bromine and iodine compounds may have a burning, biting taste.

**Iodoform,  $\text{CHI}_3$ .** Iodoform may be made by treatment of ethyl alcohol or acetone with iodine and alkali:

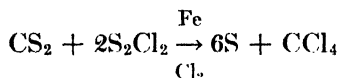


A cheaper method involves electrolysis of a solution of alcohol, an iodide, and sodium carbonate. Iodoform is a lemon-yellow solid, which crystallizes from dilute alcohol in six-sided platelets. The compound has a peculiar and very characteristic odor. Its chief use is for antiseptic purposes; in this role it is often displaced in favor of preparations in which the unpleasant odor is masked or is altogether absent (see page 642).

The formation of iodoform may be used as a test for the presence of ethyl alcohol, if one is assured of the absence of acetone, acetaldehyde, or other substances which also yield iodoform under the same conditions.

Compounds which contain the group  $\text{CH}_3\text{C}(=\text{O})\text{—}$  have this power. In their absence, a concentration of ethyl alcohol-water of 1–2000 may be detected by the iodoform test (Lieben test).

**Carbon tetrachloride,  $\text{CCl}_4$ .** This substance is produced by the complete chlorination of methane as shown on page 79. Commercially, it is made by the action of chlorine upon carbon disulfide in the presence of iodine or antimony pentasulfide, which function as carriers,\* also from the action of carbon disulfide with sulfur monochloride:



Carbon tetrachloride is a very versatile compound. It is an excellent solvent for fats and oils and often used for their extraction. Mixed with gasoline it is used by dry cleaners. As "Pyrene" it forms an effective fire extinguisher. Its vapor is heavier than air, and as it is vaporized over a fire it drifts over the flame and extinguishes it by excluding air. Phosgene may be formed and carbon tetrachloride itself is toxic; hence good ventilation should always follow the use of the substance as a fire extinguisher. Taken internally it is anti-hookworm.

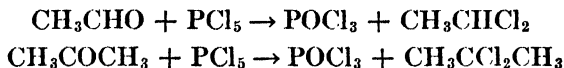
#### COMPOUNDS HAVING MORE THAN ONE CARBON ATOM

Those substances in which the halogen is concentrated about one carbon atom include such derivatives as ethylidene chloride,  $\text{CH}_3\text{CHCl}_2$ ,

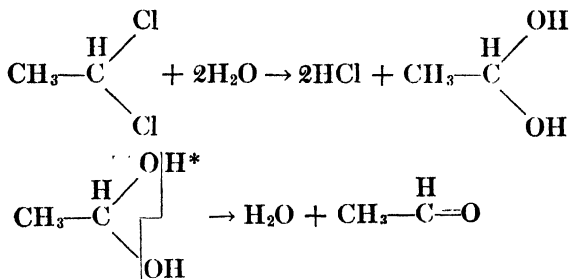
\* Other substances used as halogen carriers are metals, as iron, aluminum, etc. It is possible that the higher chlorides of these carriers ( $\text{ICl}_3$ ,  $\text{FeCl}_3$ ,  $\text{SbCl}_5$ , etc.) first react with the substance being chlorinated and are thereby changed to the normal chlorides ( $\text{ICl}$ ,  $\text{FeCl}_2$ , etc.), which by action of additional halogen again resume their more active state. Other theories have also been advanced.

and 2,2-dichloropropane,  $\text{CH}_3-\overset{\text{Cl}}{\underset{\text{Cl}}{\text{C}}}-\text{CH}_3$ . They have very little interest for

us because but few synthetic uses have been developed. Such compounds are formed by treating aldehydes and ketones with phosphorus halides as illustrated below for the compounds already mentioned:



When such compounds are subjected to hydrolysis, the original aldehyde or ketone is regenerated.

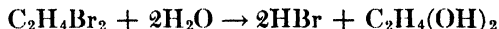


The polyhalogen compounds in which the halogen atoms find their places on separate carbons are used in many synthetic operations.

**Ethylene bromide, 1,2-Dibromoethane,  $\text{C}_2\text{H}_4\text{Br}_2$ ,** is an example of compounds of this class. As was shown on page 50, this compound is readily formed by the action of bromine upon ethylene. Its reactions resemble those of the primary alkyl halides.

Examples:

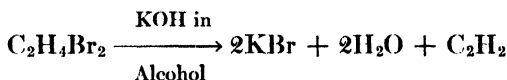
(1) *Hydrolysis.* Boiling water will slowly convert ethylene bromide to ethylene glycol:



When hydrolyzed by a strong base glycol is formed, and also vinyl bromide:

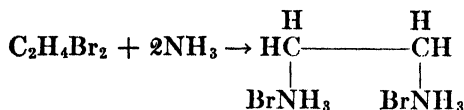


Potassium hydroxide in alcohol solution removes two molecules of HBr forming acetylene:

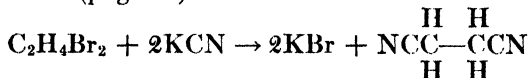


(2) *Reaction with ammonia and with potassium cyanide.* Ethylene bromide unites with two molecules of ammonia to form a di-ammonium salt:

\* When two hydroxyl groups attach to one carbon as shown here, the compound generally loses water and forms the  $\text{C}=\text{O}$  group.



The reaction with potassium cyanide is also similar in type to that of a primary alkyl halide (page 82):



Hydrolysis of the di-cyanide leads to the dicarboxylic acid, succinic acid (page 251).

Other reactions of double decomposition take place with ethylene bromide in the same manner as indicated in the above equations, however the compounds obtained have less interest for us.

Very large amounts of ethylene bromide are needed for use with tetra-ethyllead in "Ethyl fluid." Here its function is to prevent the formation of lead oxide upon decomposition of the organic lead compound. Lead bromide is formed, which escapes from the engine cylinder without further decomposition. Ethylene dichloride is of value as a fumigant, extracting agent, and lacquer solvent. When ethylene dichloride and similar compounds are treated with inorganic polysulfides, we get rubber-like substances (Thiokol resins) suitable for purposes formerly filled by rubber (see page 625). Another type of plastic (AXF) is mentioned on page 507. By choice of proper conditions one halogen atom of a compound such as 1,3-dibromopropane may be displaced at a time; hence different functions may be attached to the two ends of the chain.

#### UNSATURATED HALOGEN DERIVATIVES

**Vinyl bromide**,  $\text{CH}_2=\text{CHBr}$ , whose preparation from ethylene bromide is shown on page 87, is an example of an unsaturated halogen compound whose halogen atom is joined to a carbon holding a double bond. Such compounds do not share the typical reactions of the alkyl halides. When vinyl bromide is hydrolyzed, we do not obtain an alcohol (see page 145). Reagents which act by double decomposition with primary alkyl halides remove  $\text{HBr}$  from vinyl bromide to give acetylene:



Vinyl halides polymerize on standing, or more readily when heated, giving resins, which when hot pressed may be molded into useful shapes (Koroseal). Vinyl acetate (page 204) is similarly used (see page 506). Dichloroethylene,  $\text{ClCH}=\text{CHCl}$ , is obtained by action of chlorine with excess acetylene or reduction of acetylene tetrachloride with iron. It is an excellent solvent, also it is used as a refrigerant for air conditioning. Trichloroethylene is widely used as a solvent and extracting agent.

## FAMILY RELATIONS OF ETHYL IODIDE

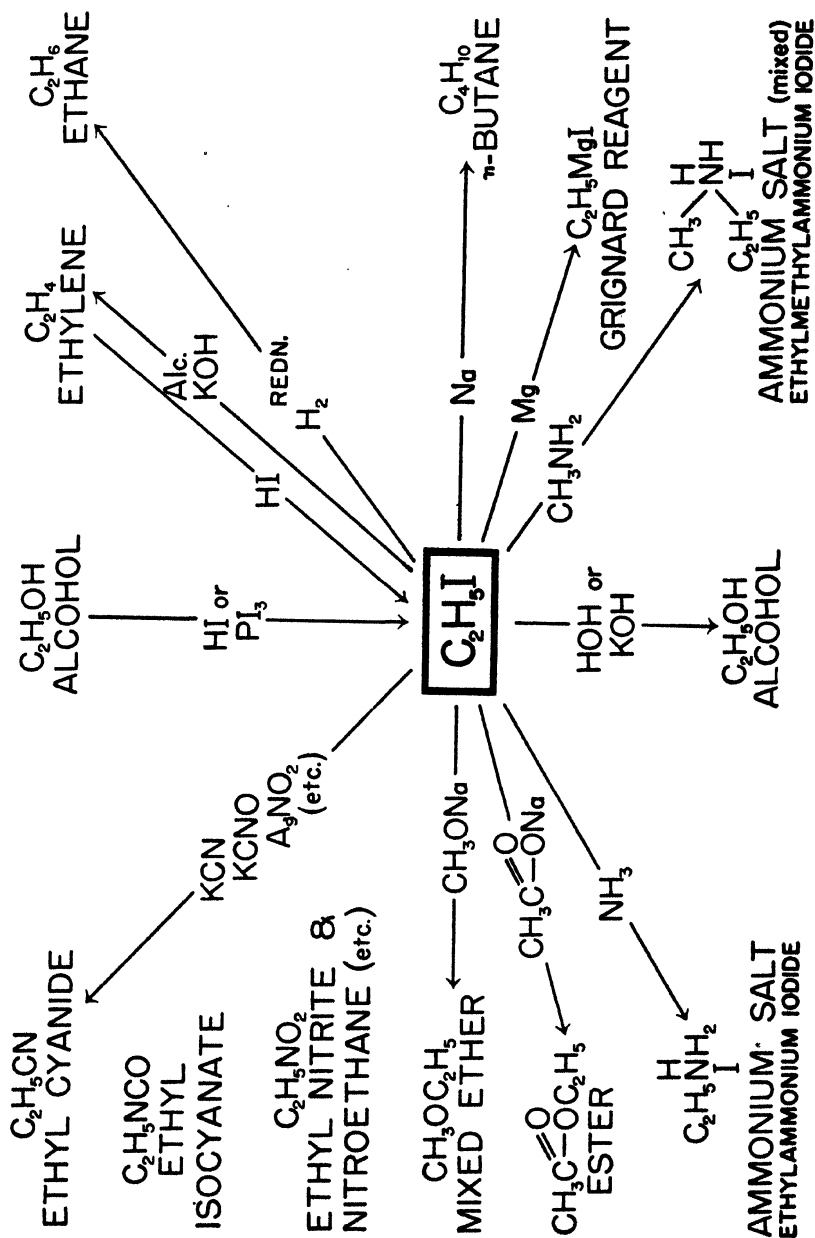


CHART III.

**Allyl bromide,\*** or **3-Bromopropene-1**,  $\text{CH}_2=\text{CHCH}_2\text{Br}$ , illustrates in its behavior those unsaturated halogen compounds whose halogen is joined to a saturated carbon atom. This compound is prepared by methods already shown for primary halides. In its reactions, it also shows a close resemblance, being more reactive on the whole than the corresponding saturated compound, propyl bromide,  $\text{CH}_3\text{CH}_2\text{CH}_2\text{Br}$  (see page 434).

#### USES OF HALOGEN COMPOUNDS

The majority of the compounds discussed have important synthetic uses, and many of the compounds, particularly those with several halogens, are excellent solvents. Several have been mentioned which are used as refrigerants; methyl and ethyl chlorides should be added to this list. If liquefied ethyl chloride is sprayed in a fine stream upon tissue, its rapid evaporation chills the tissue sufficiently to produce local anesthesia. This treatment is suitable only for minor operations. It should be mentioned that the anesthetic properties of the liquid and gaseous halogen compounds make them dangerous to handle, unless special care is exercised and ventilation is adequate. The fluorides are said to be less toxic than the other halogen compounds. Methyl bromide is employed as a fumigant, especially for packaged foods.

#### GENETIC RELATIONS

The chart on page 89 shows the genetic relations of the primary alkyl halides; to avoid crowding the page, the other halogen compounds have been left out. The student will find it to his advantage to prepare a large chart which includes all types of halogen derivatives discussed in this chapter, with their interrelations and their synthetic uses.

**Detection and Identification of Halogen Compounds.** The presence of halogen in an organic compound is detected by the Beilstein test, and the nature of the halogen is learned by conducting a sodium fusion. The ease with which the compound may be hydrolyzed gives some information regarding the structure. To learn the identity of the compound in hand one uses a scheme of analysis which is terminated by the preparation of derivatives of the compound. This is described in Chapter XI, and in the references on page 782.

#### REVIEW QUESTIONS

1. Show equations for two methods of preparing propyl iodide.
2. Give equations for the preparation of (a) 1,2-Dibromopropane; (b) Isopropyl iodide.
3. What compounds would be formed by the action of sodium upon (a) Methyl iodide? (b) Ethyl iodide?
4. How may isopropyl alcohol be made from propylene?
5. Show equations for the formation of the following from ethyl iodide: (a) A nitrile; (b) An ether; (c) an ester.

\* The radical  $\text{CH}_2=\text{CHCH}_2$ —is known as allyl (see list, page 805).

6. Give practical methods for the preparation of: (a)  $\text{CH}_3\text{Cl}$ ; (b)  $\text{C}_2\text{H}_5\text{I}$ ; (c)  $\text{CH}_3\text{CHBrCH}_3$ ; (d)  $(\text{CH}_3)_3\text{CCl}$ ; (e)  $\text{CH}_2=\text{CHCl}$ .
7. What compound results from the reaction of ammonia with ethyl chloride?
8. Show the action of water upon 2,2-dichloropropane.
9. Write equations showing the action of dilute sodium hydroxide solution upon: (a) 1,1-Dibromopropane; (b) 1,2-Dibromopropane.
10. What is the action of alcoholic KOH upon the above compounds?
11. Write the formulas of the alkylene bromides which would yield dimethylacetylene upon treatment with alcoholic KOH.
12. Write formulas of two primary, two secondary, and two tertiary hexyl chlorides. Name the compounds.
13. Write graphic formulas and names for all possible bromine substitution products of ethane.
14. Supply names for the following formulas. (a)  $\text{CH}_3\text{CHBr}_2$ ; (b)  $\text{CH}_2\text{Br}_2$ ; (c)  $\text{Cl}_2\text{C}=\text{CHBr}$ ; (d)  $\text{ClCH}_2\text{CHClCH}_2\text{Cl}$ .
15. What weight of bromine is theoretically required to react with: (a) five grams of ethylene; (b) ten grams of propylene?
16. Calculate the weight of the products of reactions of 15 (a) and (b).
17. The reaction of alcoholic KOH with a certain alkyl halide gave propylene as a product. What was the alkyl halide used?
18. A certain hydrocarbon was treated with hydrogen iodide; the resulting product was acted upon by sodium. A hydrocarbon having a boiling point of  $-0.5^\circ\text{C}$ . was produced. What was the original hydrocarbon used?
19. Give equations for the action of propyl iodide and of isopropyl iodide upon: (a) Potassium cyanide; (b) Dilute KOH solution; (c) Ammonia; (d) Sodium; (e) Alcoholic KOH solution.
20. Complete the following equations, supplying graphic formulas for the organic compounds formed thereby.
  - (a) Isopropyl bromide +  $\text{H}_2$  (catalyst)  $\rightarrow$
  - (b) 2-Bromobutane + Na (in excess)  $\rightarrow$
  - (c) 3-Iodopentane + NaOH (alcohol)  $\rightarrow$
  - (d) 2,5-Dibromopentane + NaCN (in excess)  $\rightarrow$
21. How may the groups enclosed by parentheses in the following compounds be replaced by chlorine atoms?
 

(a)  $\text{CH}_3\text{-CH}_2(\text{OH})$ ;    (b)  $\text{CH}_3(\text{H})$ ;    (c)  $\text{CH}_3\text{-CH}(\text{O})$ .
22. Write equations indicating how to make isopropyl bromide from propyl bromide.
23. Name the compound at the bottom of page 86 as a derivative of methane.
24. Chloroform may add to certain other compounds, as Cl and  $\text{HCCl}_2$ . Show what would be formed by its addition to tetrachloroethylene. Name the new compound.
25. An alkyl halide, when poured into water, sinks. What does this show? What further work must be done to identify the compound?
26. What is the Beilstein test? For what purpose is it used?
27. Describe the laboratory tests which prove that an organic compound contains halogen.
28. In making methyl chloride from methane and chlorine which material should be used in excess? Why?
29. What advantage lies in the use of gaseous HCl in making EtCl from EtOH?
30. The statement is made early in the chapter that in a series of alkyl halides with the same halogen atom, the density decreases as the number of carbon atoms increases. Explain this phenomenon.
31. In a certain case an alkyl iodide is hard to prepare by direct means while the chloride may easily be made. The chloride, however, reacts very slowly in further experiments. How might one solve this difficulty?



32. Do alkyl halides ionize? Describe a laboratory test which would furnish an answer to this question.
33. Mention various reasons why the organic halogen compounds used in industry as solvents are chlorides rather than bromides or iodides.
34. Why are organic iodides often used in the laboratory in preference to the chlorides?
35. Why is the electrolytic method for preparing  $\text{HCl}_3$  cheaper than that illustrated on page 86?
36. A substance containing C, H, and halogen is heavier than water. To what halogen series may it belong?
37. The laboratory instructor has on hand an ample supply of the following chemicals for class use: water,  $\text{H}_2\text{SO}_4$ ,  $\text{EtOH}$ ,  $\text{MnO}_2$ ,  $\text{NaCl}$ . What organic halogen compounds can he assign for preparation by the class? Write a sequence of equations showing the preparation of each compound.
38. What test would distinguish allyl bromide from propyl bromide? Describe it.
39. Which would be more likely to polymerize, vinyl chloride or ethyl chloride? Why?
40. List organic halogen compounds used in medicine and give specific medical uses for each one.
- (R)41.\* Let A = ethyl iodide and B = ethyl alcohol. (a) Which of the following reagents: [ $\text{H}_2\text{SO}_4$  (cold, concentrated),  $\text{HI}$ ,  $\text{Na}$ ,  $\text{PCl}_3$ ,  $\text{NaCN}$ ,  $\text{NaOH}$  solution] may be used to convert A to B?
- (b) Which reagent may be used to convert B to A?
- (c) Which reagents will react with A, not with B?
- (d) Which reagents will react with B, not with A?
- (e) Which reagents will react with both A and B?

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\* See footnote, page 46.

## CHAPTER V

### ALCOHOLS. THIOALCOHOLS

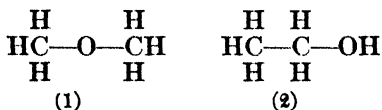
Among the numerous naturally-occurring organic compounds which are built up of the elements C, H, and O (see table on page 804), the alcohols form the simplest class. In nature their representatives are found both free and in the form of compounds (esters), in which their individuality may be somewhat masked or altered. From both the physical and chemical standpoints, alcohols are exceedingly useful compounds. The great efficacy of grain and wood alcohols in varied uses has made these substances as familiar to the general public as to the chemist, who would find it impossible to carry on his work without their aid. Ethyl alcohol is produced in greater volume than any other organic chemical.

By their mode of formation and their reactions, we find the alcohols to be the hydroxy derivatives of the hydrocarbons. One or more hydroxyl groups may be present in an alcohol; thus we have monohydroxy alcohols, also polyhydroxy compounds. The latter class includes dihydroxy, trihydroxy alcohols, etc. They will be considered later.

As said above, alcohols are hydroxy derivatives of the hydrocarbons; it is often useful to picture them as alkyl derivatives of water. This conception is illustrated in the table on page 805 and will be referred to again.

#### STRUCTURE OF ETHYL ALCOHOL

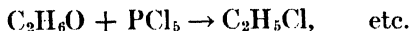
Following is a brief review of the method by which the structures of alcohols have been determined. The molecular formula of ethyl alcohol, the best known of the series, determined by the usual methods, is  $C_2H_6O$ . If we give C and H their usual valences of four and one, two graphic formulas may be made, (1) and (2):



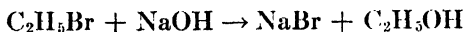
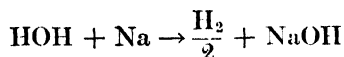
Now alcohol reacts with metallic sodium, but when it does so only 1 g. of hydrogen gas is liberated from 46 g. of alcohol, no matter how great an excess of sodium we use. In other words, only one hydrogen of the molecule is substituted. This favors formula (2) as has already been explained on page 16.

We can make alcohol from ethyl bromide and potassium hydroxide solution, forming potassium bromide as a by-product. Again formula (2)

receives support while (1) does not. Also when we treat alcohol with  $\text{PCl}_5$ , the compound loses one oxygen *and* one hydrogen while gaining one Cl:



Quite evidently the oxygen and one of the hydrogens are connected and formula (2) is again supported. By this time it is apparent that alcohol is actually derived from water as suggested above, and this is not merely a device for classifying the compound. The following equations represent the reactions which bear out this statement:



The structures of organic compounds are determined from examination of the reactions of the compounds or of the methods by which they are made.

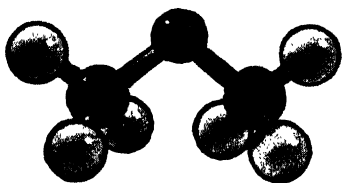


FIG. 21.

Isomers of  
formula  
 $\text{C}_2\text{H}_6\text{O}$

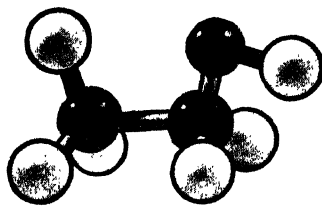


FIG. 22.

Ordinarily it is necessary to use information from both sources as was done here. In the case treated on page 31 it was not convenient to use the reactions of the compounds in solving the problem of structure.

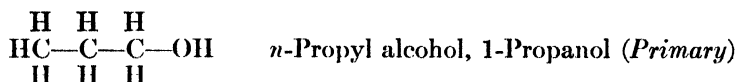
### CLASSIFICATION OF ALCOHOLS

The general formula of an alcohol is  $\text{ROH}$ . The "key atom" is oxygen, as halogen is the key atom of the compounds discussed in the previous chapter. An alcohol is then a two-functioned compound, the functions being (1) hydrocarbon chain\* and (2) hydroxyl group. The reactions of function (1) have been studied; new material in this chapter concerns the behavior of the OH group when joined to R. The radical  $\text{R}^\dagger$  may be alkyl, alkylene, or acetylenic in its structure, according to whether we consider saturated or unsaturated alcohols. Among these series, the saturated alcohols are the most important, and they will be taken up first in order.

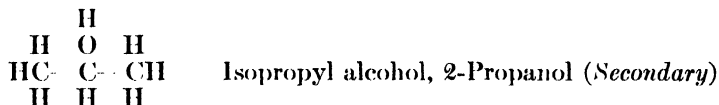
Saturated alcohols fall into the three divisions *primary*, *secondary*, and *tertiary*, as the hydroxyl group is attached to a primary, secondary, or tertiary carbon, respectively. Examples of these types are the following:

\* See footnote, page 75.

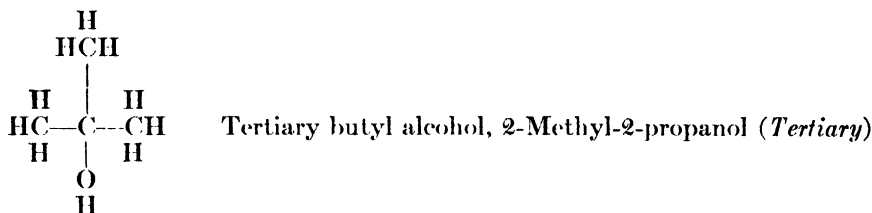
† The letter R may stand for *any* radical, but at present we are limited to the alkyl, ethylenic, and acetylenic types. Names of radicals are often abbreviated, Me for methyl, Et for ethyl, Pr for propyl.



All primary alcohols have the group:  $-\text{CH}_2-\text{OH}$



All secondary alcohols have the group:  $\begin{array}{c} \diagup \text{H} \\ \text{C}-\text{OH} \\ \diagdown \end{array}$



Tertiary alcohols have the group:  $\begin{array}{c} \diagup \\ \text{C}-\text{OH} \\ \diagdown \end{array}$

### PHYSICAL PROPERTIES OF SATURATED ALCOHOLS

The normal monohydroxy alcohols which have short carbon chains are mobile, colorless liquids, miscible in all proportions with water. The solubility in water lessens as the series is ascended, and we find at the same time an increase in viscosity together with the usual rise in boiling and melting points. Amyl alcohol,  $\text{C}_5\text{H}_{11}\text{OH}$ , is only partly miscible with water, and has an oily consistency. Higher members (from  $\text{C}_{12}$  on) are waxy colorless solids, resembling the paraffins in appearance.

Several of the lower members, notably crude butyl and amyl alcohols, and ordinary methyl alcohol, have a pronounced and disagreeable odor, but in general alcohols are practically odorless. The lower members give a burning sensation in the mouth, but are tasteless. An increase in the number of OH groups in an aliphatic alcohol causes an increasing sweet taste. Note that the glycols and glycerol are sweet and that simple sugars have a number of OH groups per molecule. Table 8 shows the melting points, boiling points, and densities of members of the series of normal primary alcohols.

This table shows the regular difference in boiling points between succeeding members of the series, which, after ethyl alcohol, is about  $19^\circ$ . Another fact illustrated by the table is often met in the study of a homologous series, i.e., the physical properties of the first member do not fall into line with those of the rest of the series. In some instances (as with aldehydes and

acids) the chemical properties of the first member are also out of line. In ascending the series the difference between boiling points of members decreases. If we agree that the rise in boiling point as we ascend the series is caused by the increase of 14 points in molecular weight due to the  $\text{CH}_2$  increment, we will expect to find this effect most pronounced at the beginning of the series. The molecular weight of ethyl alcohol is 46 and the addition of  $\text{CH}_2$  increases this by 30%. Later in the series the rise of boiling point should not be so great. The molecular weight of nonyl alcohol is 144 of which 14 is only 10%. Other series will show this same phenomenon.

TABLE 8.—NORMAL PRIMARY ALCOHOLS

Name of radical	Formula	M.p., °C.	B.p., °C.	Sp. g., 20°/4°	Ht. of comb.	Calcu- lated No. of isomers (all types)
Methyl.....	$\text{CH}_3\text{OH}$	— 97.8	64.5	0.792	170.9	1
Ethyl.....	$\text{C}_2\text{H}_5\text{OH}$	—112.0	78.5	0.789	328	1
Propyl.....	$\text{C}_3\text{H}_7\text{OH}$	—127.0	97.8	0.804	480.5	2
Butyl.....	$\text{C}_4\text{H}_9\text{OH}$	— 70.9	117.0	0.810	639	4
Amyl.....	$\text{C}_5\text{H}_{11}\text{OH}$	— 78.5	137.9	0.817 <sup>20/20</sup>	794	8
Hexyl.....	$\text{C}_6\text{H}_{13}\text{OH}$	— 51.6	155.8	0.820 <sup>20/20</sup>	950.6	17
Heptyl.....	$\text{C}_7\text{H}_{15}\text{OH}$	— 34.6	175.8	0.824	1104.9	39
Octyl.....	$\text{C}_8\text{H}_{17}\text{OH}$	— 16.3	194.0	0.827	1262	89
Nonyl.....	$\text{C}_9\text{H}_{19}\text{OH}$	— 5.0	215.0	0.828	1420.2	211
Decyl.....	$\text{C}_{10}\text{H}_{21}\text{OH}$	+ 7.0	231.0	0.829	1576.9	507
Hendecyl.....	$\text{C}_{11}\text{H}_{23}\text{OH}$	19.0	131.0 <sup>15</sup>	0.833	.....	1238
Dodecyl.....	$\text{C}_{12}\text{H}_{25}\text{OH}$	24.0	259.0	0.831*	.....	3057
Tetradecyl.....	$\text{C}_{14}\text{H}_{29}\text{OH}$	38.0	167.0 <sup>15</sup>	0.824*	.....	19,241
Cetyl.....	$\text{C}_{16}\text{H}_{33}\text{OH}$	49.3	190.0 <sup>15</sup>	0.818*	2540.5	124,906
Octadecyl.....	$\text{C}_{18}\text{H}_{37}\text{OH}$	58.5	210.5 <sup>15</sup>	0.812*	.....	830,219

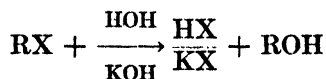
\* At M.p.

### PREPARATION OF SATURATED ALCOHOLS

**Primary Alcohols.** Type  $\text{R}-\overset{\text{H}}{\underset{\text{H}}{\text{C}}}-\text{OH}$ . A number of methods are known

by which these compounds may be made, of which the following are perhaps of the greatest interest and importance.

(1) Preparation by treatment of an alkyl halide with water or a base:



The amyl alcohols in particular are prepared on a large scale from the

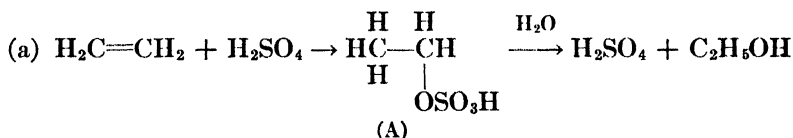
chloropentanes by this method. As will be noted by reference to page 83, alkyl iodides react more readily in this manner than do the bromides or the chlorides. Primary halides give the best yields of alcohols. Secondary and tertiary halides give increasing yields of olefins in the order named.

(2) The reduction of an aldehyde in the presence of hydrogen produces the corresponding alcohol:

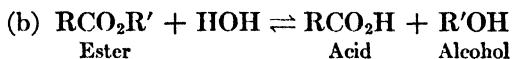


For reduction of esters to alcohols, see page 206.

(3) The addition product of ethylene and sulfuric acid when hydrolyzed yields ethyl alcohol:



All olefins go through this reaction, but those higher than ethylene give secondary or tertiary alcohols.\* About 35% of the ethanol of commerce is made in this way. A compound such as (A) above is called an ester, and this equation shows one application of a general method of making alcohols from esters. The type formula for the ester of an *organic acid* is  $\text{RCO}_2\text{R}'$ , and any such compound upon hydrolysis will yield an alcohol:

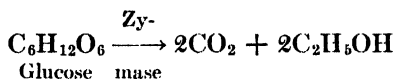


Many such esters occur in nature; it is at times possible by their hydrolysis to secure alcohols which would be difficult of preparation by other means (see esters, page 205, also page 736).

(4) By the use of the Grignard reaction, described on page 572, alcohols of all types may be prepared.

(5) Several alcohols are formed by yeast fermentation of starchy materials or sugars. As a source of starch a cereal such as corn or barley may be used, or potatoes or beets. The starch is progressively broken down due to the action of the enzymes contained in the yeast and malted barley which is added (see page 740). The enzyme diastase of the malt converts starch to maltose, which by the action of maltase of the yeast reverts to a simple sugar called glucose. Yeast also contains zymase, which aids the change of glucose to ethyl alcohol and carbon dioxide:

\* It is possible that in many cases the sulfuric acid does not form an ester, but instead catalyzes the addition of H and OH to the olefin.



At the same time, other alcohols (propyl, butyl, amyl, and higher alcohols, also glycerol) are formed, together with other substances, such as aldehydes and esters. Certain of these substances are probably made not from sugar, but from other compounds which occur in the original starch, or are added to promote the growth of the yeast. The commercial source of ethyl alcohol is molasses from sugar mills, which is treated with yeast as outlined above. See flow sheet, page 789. The fermentation process is used to make most of the ethyl alcohol of commerce. A continuous fermentation process to replace the batch process is a recent invention. (See Reference 5, page 119.)

When ethyl alcohol is made on the large scale by fermentation the carbon dioxide produced is not wasted. This has a ready sale as "Dry Ice" in solid form, or is distributed in tanks as compressed gas. The alcohol in the fermentation mass is dilute (about 10%) and is concentrated by fractional distillation. The concentration cannot be raised to 100% however, as alcohol and water form an azeotropic mixture in which the alcohol percentage is 95.57% by weight. Alcohol of commerce is about 95% by volume.

"Absolute" alcohol may be obtained from the alcohol of commerce by chemical means. In the laboratory last traces of water are usually removed by the use of calcium oxide or magnesium methoxide, or sodium and ethyl phthalate.\* (See Fieser, *Experiments in Organic Chemistry*, Heath, 1941, page 359.)

In industry the 95% alcohol is distilled with benzene. A ternary mixture of the water, alcohol, and benzene has a boiling point of 64.8°. When all water has distilled, the binary mixture of alcohol and benzene boils at 68.2° until the benzene has all distilled. One hundred per cent alcohol remains. On the small scale (batch method) very little alcohol is left in the still, but by using large-scale equipment and continuous distillation this is a practical method.

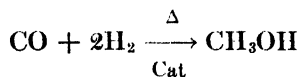
To prevent its use for drinking, alcohol is denatured; thus the usual tax for beverages is avoided. Many different denaturants are used; crude methyl alcohol from wood distillation, pyridine, and kerosene are common for this purpose.

*Methyl alcohol* is prepared commercially to some extent by the destructive distillation of wood. A mixture of substances is obtained by this process

\* Calcium chloride cannot be used since it unites with the alcohol to form  $\text{CaCl}_2 \cdot 4 \text{EtOH}$ . Other salts unite in a similar way with ethyl alcohol, methyl alcohol, etc. These salts, analogous to the hydrates formed by water, should be called alcoholates, and the name alkoxides should be used for the ROMetal salts. This change of name is apparently taking place in the literature at the present time.

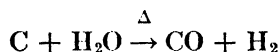
(tar, acetic acid, acetone, methyl alcohol) from which the alcohol may be removed. Methyl alcohol may also be formed by the general methods which are shown above (save numbers (3a) and (4)).

It is now being made on a commercial scale in 99.9% purity by a reaction between carbon monoxide and hydrogen:



The process consists of heating the gases to a temperature of about 450° at a pressure of about 200 atmospheres, in the presence of a catalyst (zinc oxide, zinc chromite, or zinc oxide and copper).\*

The importance of this method lies in the fact that a mixture of equal parts of carbon monoxide and hydrogen is easily made from the action of steam upon hot carbon (Water gas).

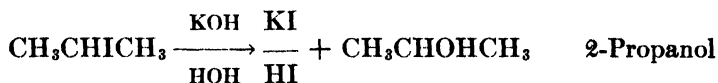


The additional hydrogen needed is readily prepared by the electrolysis of water. The method is important from quite another standpoint, in that variations of temperature, pressure, and the nature of the catalyst employed, allow the production of a wide range of organic compounds (alcohols, acids, dimethyl ether, esters, etc.). Important developments will undoubtedly follow as this reaction receives further study.

*n*-Butyl alcohol, for which there is a large market, is made by the fermentation of starch. The process, originally developed to produce acetone during the War, actually gives larger yields of butyl alcohol than of acetone. By-products, all of which are useful, are hydrogen and carbon dioxide (from which methyl alcohol is made), acetone, and ethyl alcohol. Butyl alcohol is largely used in the compounding of lacquers. See page 790 for flow sheet.

**Secondary Alcohols.** Type  $\text{RR}'\text{CHOH}$ . These alcohols may be prepared by the following methods:

(1) By the treatment of a secondary alkyl halide with water or a base:



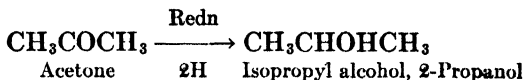
See comment, page 81.

(2) By the use of the Grignard reaction (see page 572).

\* About 7,000,000 gallons of synthetic methanol were produced in this country in 1930. About the same amount was produced by distillation of wood. 1939 production (synthetic) was 34,146,669 gallons. Methanol prices per gallon were, 1927, \$1.10; 1939, \$0.27.



(3) By the reduction of the proper ketone in the presence of hydrogen ion:



(4) The gases formed in the cracking of petroleum contain notable amounts of olefins, which may be removed by the action of sulfuric acid. They react with the acid as indicated (for ethylene) on page 97. The resulting esters upon hydrolysis yield secondary alcohols. Isopropyl, secondary-butyl, -amyl, alcohols are made by this method.

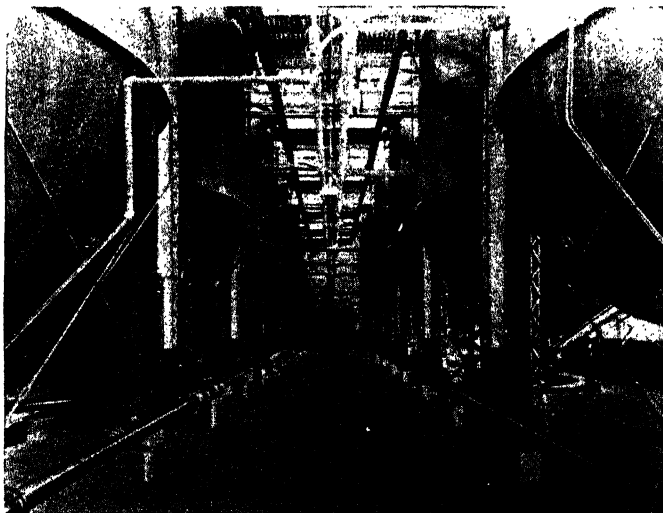


FIG. 23.—Lower level view of 50,000 gallon fermentation tanks used in production of butyl alcohol, acetone, and ethyl alcohol from corn starch. (*Commercial Solvents Corporation.*)

**Tertiary Alcohols.** Type  $\text{RR}'\text{R}''\text{COH}$ , are best prepared by means of the Grignard reaction as described on page 573.

This method is general. Specific alcohols may be made more cheaply by some other method. Thus tertiary butyl alcohol is made by the hydration of isobutylene with intermediate use of sulfuric acid, as shown for ethyl alcohol in method (3).

#### REACTIONS OF SATURATED ALCOHOLS

All alcohols contain the hydroxyl group, and will therefore have more or less similar reactions. That is, the reactions of primary alcohols (or secondary) will be more or less similar. On account of the differing structures of the carbon skeletons in primary and secondary (tertiary) alcohols, we must expect certain differences between the reactions of compounds of

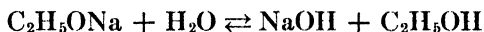
the several classes. The reactions may be grouped under the heads substitution, oxidation, and dehydration for the saturated alcohols.

(1) *Replacement of hydrogen.* The hydrogen of the hydroxyl group of an alcohol may be replaced by:

(a) An active metal. In this way salts called alkoxides are formed. Specific salts are named for the particular alcohol used, as methoxide, ethoxide, etc.

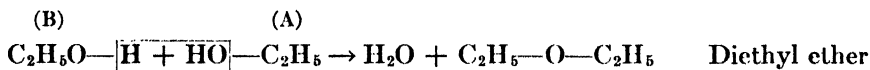


In this reaction primary alcohols are much more active than secondary, and the tertiary alcohols are very sluggish. The salt formed in the reaction may be isolated if the metal is added to the pure alcohol. In presence of water such salts are hydrolyzed, since water is more highly ionized than are these alcohols.

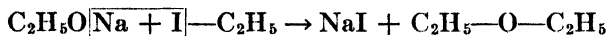


However, if the water is removed, it is quite possible to cause the above reaction to proceed to the left and to form the alcohol salt in good yield. Several of the alkoxides are employed in the synthesis of organic compounds (see page 123).

(b) Hydrogen of the hydroxyl group may be replaced by an alkyl group in two ways. When an alcohol is treated with a dehydrating agent, it is possible for two molecules of alcohol to lose one molecule of water cooperatively:



By this reaction the alkyl group of alcohol (A) is substituted for the hydrogen atom of alcohol (B). The same effect is secured when an alkoxide reacts with an alkyl halide:



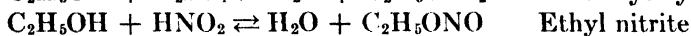
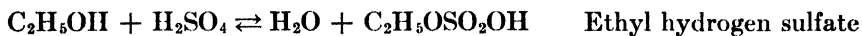
By either method, an ether is formed. Both of the above reactions will therefore be discussed in the chapter on ethers.

(c) Replacement by an acid group (organic) by the use of an acid, acid anhydride, or acid chloride. Compounds called esters are made in this way. These compounds are more particularly discussed on page 197, and the following pages.

In the reactions in which esters are formed the by-product is water. Hydrogen is lost by the alcohol and hydroxyl by the acid. Therefore the primary alcohols undergo the reactions most readily and tertiary least readily. Tertiary alcohols excel in reactivity where OH group is to be substituted and primary where H of the OH group is to be lost.

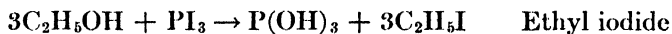
\* See footnote, page 98.

Examples of esterification with inorganic acids are shown in the following equations:

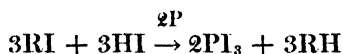


The reaction with hydrogen iodide is seen to produce an alkyl halide, as does treatment of the alcohol with phosphorus iodide.

(2) *Replacement of hydroxyl group.* The OH group of alcohols may be replaced by a halogen atom. This is accomplished by the use of the phosphorus halide:

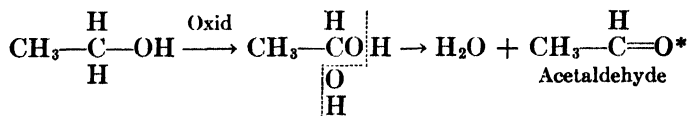


(Note that the use of a free halogen would give another product; page 146, aldehydes.) The same type of replacement is brought about by the use of a halogen acid (equation, page 79). When hydrogen iodide is used there is a possibility that the alkyl halide will be reduced to an alkane by an excess of this reagent:

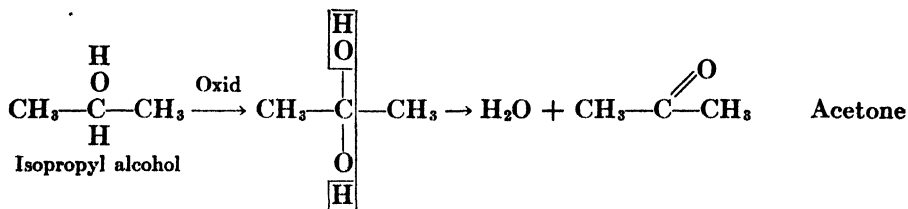


The replacement of a hydroxyl group takes place most easily with tertiary alcohols, and with decreasing ease with secondary and primary alcohols. The ease of exchange with a tertiary alcohol is well illustrated by the fact that tertiary butyl chloride may be made in good yield by merely shaking tertiary butyl alcohol with concentrated hydrochloric acid for a few minutes.

(3) *Oxidation of alcohols.* The oxidation of a primary alcohol yields the corresponding aldehyde:



This oxidation may go farther to produce the corresponding acid (page 140). Secondary alcohols on oxidation yield substances called ketones (page 138).

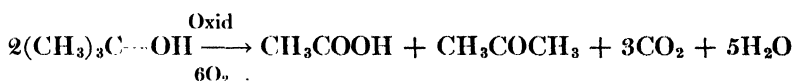


\* Compounds in which two OH groups are joined to one carbon atom generally lose water as shown in this case.

The ketone on further oxidation yields a mixture of acids (page 153).

Tertiary alcohols break down on oxidation to give in general a mixture of acids and ketones, each having fewer carbons than the alcohol.

Example:



**Digression.** Since ethyl alcohol has two carbons open to attack it might be supposed that its oxidation would yield  $\text{HOCH}_2\text{CH}_2\text{OH}$ ; however we do not observe the formation of this compound. Similarly in the oxidation of isopropyl alcohol we do not obtain  $\text{HOCH}_2\text{CHOHCH}_3$ . The carbon atom of ethyl alcohol which holds the OH group having already been partially oxidized is much more vulnerable to further oxidation than the carbon of the methyl group. We have here an example of a general rule that "action tends to proceed where initiated." This rule like others has its exceptions but is still quite useful in making predictions of possible reactions. At a later point an explanation will be attempted (page 172).

(4) *Action of halogens on primary alcohols.* Substances such as chloroform, iodoform, chloral, are formed from ethanol. The reactions concerned are more pertinent to the aldehydes and will be found in that chapter (page 146).

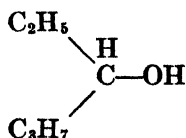
(5) *Formation of olefins from alcohols.* As was shown on page 53, ethylene may be formed by the dehydration of ethyl alcohol by sulfuric acid or phosphorus pentoxide:



Higher alcohols also lose water by such treatment to form compounds of the olefin series. The alcohol may be heated alone or with a dehydrating agent as suggested. Ease of dehydration is indicated by the temperature needed to promote the reaction. Tertiary alcohols are most easily dehydrated as would be expected, secondary and primary following in the order given.

## NOMENCLATURE OF ALCOHOLS

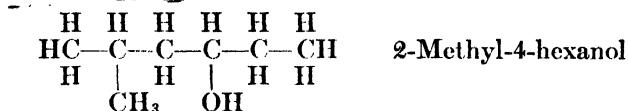
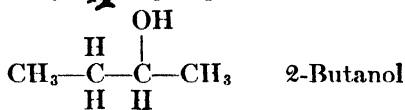
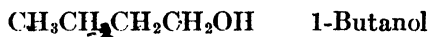
Alcohols are commonly named after the hydrocarbon radical associated with hydroxyl, as methyl, ethyl, isopropyl, etc. They may also be named as derivatives of methyl alcohol, which has the name *carbinol*.\* Thus



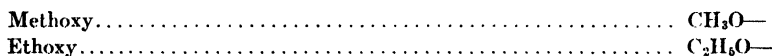
\* It is suggested (1937) that this be called *methanol*.

may be called ethylpropylcarbinol, as it represents methyl alcohol (carbinol), with ethyl and propyl groups substituted for two of its hydrogens. Another method (I.U.C. system) is to add "ol" to the name of the saturated hydrocarbon group. (The name-ending *ol* indicates the hydroxyl group.) A number is used to show on which carbon the group is found.

Examples:



A new radical is introduced with the alcohols, known in general as the alkoxy radical, RO—. Examples are:



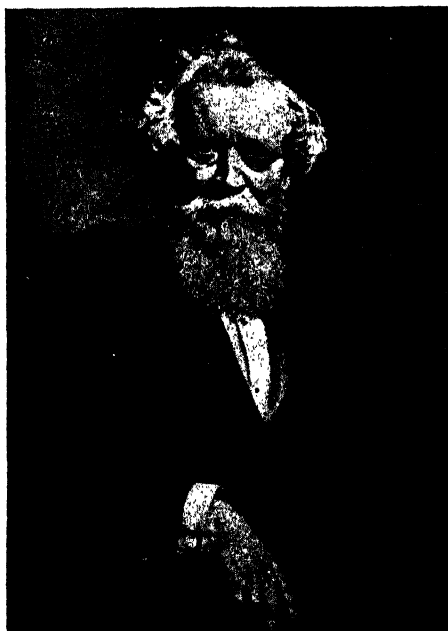
The following table of butyl and amyl alcohols shows the nomenclature used.

TABLE 9.—BUTYL AND AMYL ALCOHOLS

Name		Formula	M.p., °C.	B.p., °C.	Sp. g., 20°/4°
Common	Official				
<i>n</i> -Butyl.....	1-Butanol	$\text{C}_4\text{H}_9\text{OH}$	— 79.7	117.0	0.810
Isobutyl.....	2-Methyl-1-propanol	.....	—108.0	107.3	0.802
<i>sec</i> -Butyl.....	2-Butanol	.....	.....	99.5	0.808
<i>tert</i> -Butyl.....	2-Methyl-2-propanol	.....	+ 25.5	82.9	0.786
<i>n</i> -Amyl.....	1-Pentanol	$\text{C}_5\text{H}_{11}\text{OH}$	— 78.5	137.9	0.817 <sup>20/20</sup>
Isoamyl.....	3-Methyl-1-butanol	.....	—117.2	132.0	0.812
Active amyl.....	2-Methyl-1-butanol	.....	.....	123.0	0.816
<i>sec</i> -Amyl.....	2-Pentanol	.....	.....	119.5	0.809 <sup>20/20</sup>
Diethylcarbinol.....	3-Pentanol	.....	.....	115.6	0.815 <sup>25</sup>
<i>tert</i> -Amyl.....	2-Methyl-2-butanol	.....	— 11.9	101.8	0.809
<i>tert</i> -Butylcarbinol.....	2,2-Dimethyl-1-propanol	.....	+ 53.0	114.0	0.819
Methylisopropylcarbinol.....	3-Methyl-2-butanol	.....	.....	114.0	0.819 <sup>19</sup>

Inspection of this table will show the effect of structure upon boiling point. The normal compound in the series has the highest boiling point and that one with the most branched structure the lowest boiling point (also the greatest water solubility and the least density). The same rule holds, with a few exceptions in some instances, for other series of organic compounds (see page 38).

AUGUST W. VON HOFMANN. (1818-1892, German.) Hofmann was an outstanding teacher and writer. He was led to the study of chemistry by the influence of Liebig's teaching. Hofmann worked principally with the amines, triphenylmethane dyes, isonitriles, mustard oils. See *Am. Chem. J.*, **14**, 329 (1892), *J. Chem. Soc. (London)*, **69**, 575 (1896); also this book, pages 305, 682.

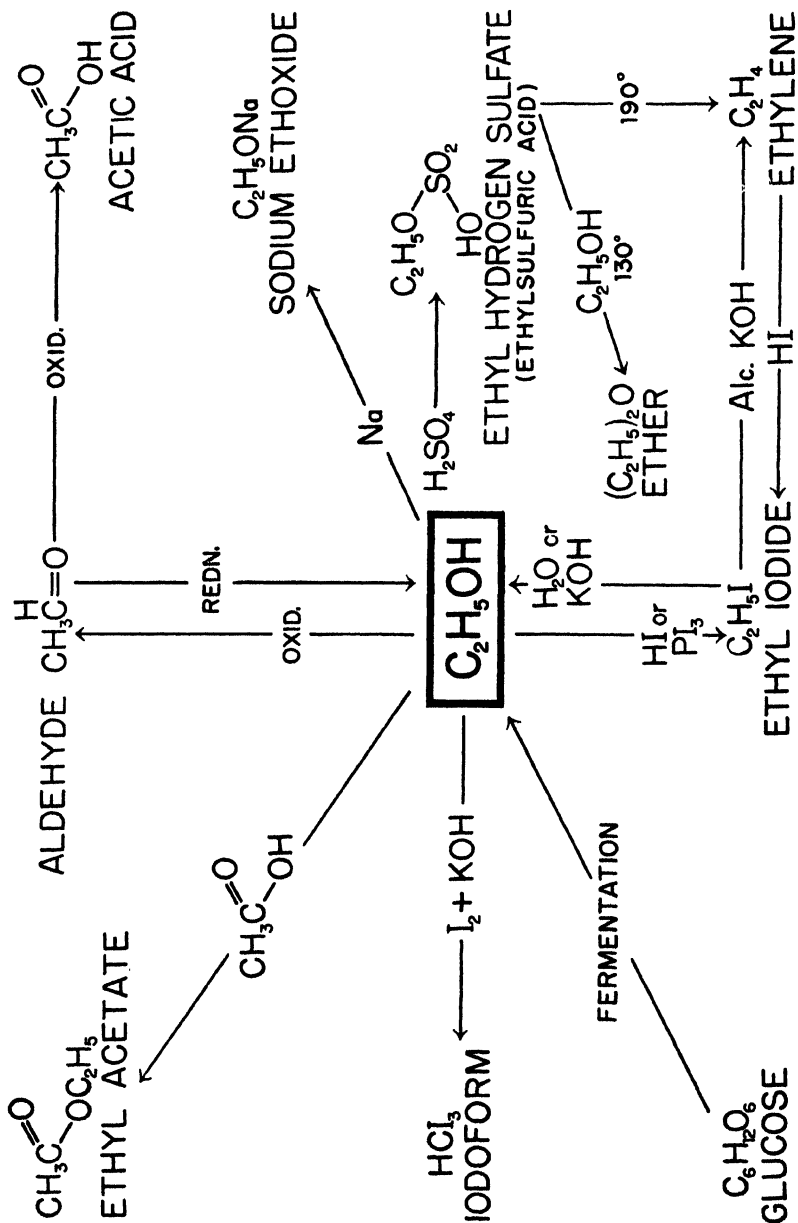


*Berichte* **51**, (1918).



ADOLPH W. H. KOLBE. (1818-1884, German.) A prolific worker in organic synthesis. He is credited with: synthesis of acetic acid, of acids from alcohols with one less carbon, electrolysis of organic acids to yield hydrocarbons, synthesis of salicylic acid and recognition of its antiseptic value. Kolbe was the author of influential texts in both organic and inorganic chemistry. See *J. Chem. Soc. (London)*, **47**, 323 (1885); also this book, pages 165, 500.

## FAMILY RELATIONS OF ETHYL ALCOHOL



## USES OF ALCOHOLS. PHYSIOLOGICAL DATA

The alcohols are exceedingly useful compounds, not alone to the chemist, but to the manufacturer and the general public as well. Methyl alcohol is widely used as a solvent for gums, shellac, varnishes; as a raw material for synthesis, especially for the production of formaldehyde; as a methylating agent (to introduce the methyl group into compounds); as a denaturant for ethyl alcohol; as an antifreeze for automobile cooling systems; as a solvent. Ethyl alcohol is used in the preparation of tinctures, etc., for medicinal purposes, paint removers, cleaning solutions, metal lacquers, and in manifold other applications of this kind. Ethyl alcohol burns with a clean hot flame, and may be used as a source of heat; likewise as a source of power in internal combustion engines. It is used in large quantities for making antifreeze solutions for automobile radiators. About 127,000,000 gallons of denatured alcohol were used in this country in 1940. Present rate of production is about 500,000,000 gallons yearly; about half of the output is devoted to the synthesis of butadiene (1943).

Sponged on the skin alcohol has a beneficial effect, and in 70% concentration is a good germicide. Taken internally in small doses it gives effects which have caused it to be called a stimulant, though it may not actually be one. It may be used both in the role of food and of stimulant in medical treatment. With large doses there is a drop in blood pressure, a decided narcotic action, followed by a paralysis which may end in death. The tribromo derivative,  $\text{Br}_3\text{CCH}_2\text{OH}$  (Avertin), has been used somewhat as a general anesthetic (by rectal injection).

Methyl alcohol is a dangerous compound taken either externally or internally. Ingestion of as little as 10 cc. may cause blindness. One should be very careful not to breathe the vapor during distillations, crystallizations, and other use.

Alcohols higher than ethyl rise in toxicity with increased length of carbon chain. Isopropyl alcohol is used in place of ethyl alcohol in some of its roles as the former cannot be used as a beverage. It is a raw material for the synthesis of acetone and a denaturant for ethanol. Higher alcohols are largely used as solvents and to make their esters which may also function as solvents. Octyl alcohol and several higher in the series are used in perfumes. Lauryl alcohol and other alcohols made from fats are used to make modern detergents (page 220).

Synthetic uses of the alcohols will appear at frequent intervals in this book, as they are very serviceable to the chemist in the construction of a great variety of useful organic compounds.

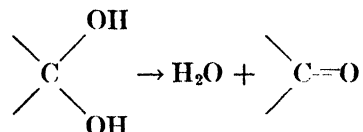
## POLYHYDROXY ALCOHOLS

Numerous alcohols are known containing from two to six or more hydroxyl groups, some of which occur in nature (several hexahydroxy



alcohols are found in the sap of certain trees); others have been synthesized in the laboratory. In our study of the polyhydroxy alcohols, we shall confine our notice to glycol and glycerol, examples of the classes of di- and trihydroxy alcohols, whose behavior is typical of that of other compounds of these groups.

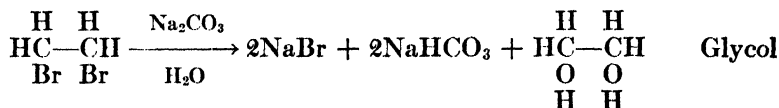
The compound  $\text{H}_2\text{C}(\text{OH})_2$  which would be expected to form the first member of the series of dihydroxy alcohols, does not exist. As was noted on page 102, a union of two OH groups with one carbon is unstable and tends to lose water:



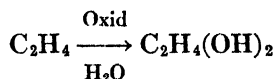
Thus, the dihydroxy alcohols will have at least two carbon atoms. The simplest representative is Glycol,  $\text{C}_2\text{H}_4(\text{OH})_2$ .

**Glycol.** The name glycol is applied to alcohols having two OH groups and also to the first member of this series (sometimes known as ethylene glycol).<sup>\*</sup> As indicated by the name (Greek,  $\gamma\lambda\upsilon\kappa\omicron\sigma$ , sweet) the compound has a sweetish taste. It is a colorless liquid, quite soluble in water, useful as a solvent,<sup>†</sup> for antifreeze solution (Prestone), as a preservative, and as a cooling liquid for aeroplane motors. The dinitrate is an explosive used in conjunction with nitroglycerin. Ethylene glycol is reported to be as toxic as methanol when taken internally.

Glycol may be prepared by method (1) shown for the primary alcohols, that is, by the hydrolysis of a hydrocarbon dihalide:



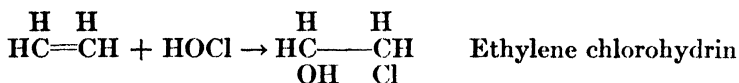
The compound may also be formed by the mild oxidation of ethylene in water solution as was pointed out on page 55.



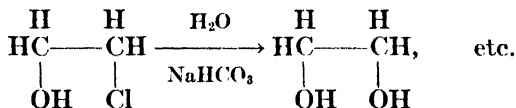
Commercially this oxidation is effected by causing an addition reaction to take place between ethylene and hypochlorous acid:

<sup>\*</sup> Latest suggested name for the compound is 1,2-ethanediol.

<sup>†</sup> The ethers of glycol are also excellent solvents, finding extensive use in the lacquer industry. See also page 128.



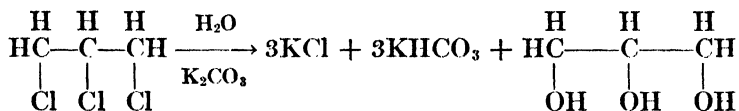
The resulting ethylene chlorohydrin is next hydrolyzed to yield glycol:



The chlorohydrin may also be changed to ethylene oxide (page 112) which is next hydrolyzed to glycol in a separate operation.

**Glycerol, Glycerin, 1,2,3-Propanetriol.** Glycerol resembles glycol in appearance, being a colorless syrupy liquid. Like glycol and other polyhydroxy alcohols, glycerol has a sweet taste. The properties of glycerol are such as to give it a wide usefulness in the arts. It is miscible with water and with alcohol in all proportions, and is an excellent solvent. Because of its softening action upon the skin, and general solvent powers, it wins a place in the preparation of cosmetics. Glycerol is very hygroscopic, and thus is used in preserving tobacco to keep it from drying out, and as an ingredient, of inks for use on stamp pads. It is employed as a sweetening agent for beverages, also it finds application in many perfumes and medicines (it is non-toxic). See also, nitroglycerin, page 200, plastics, page 534.

Glycerol is obtained commercially by the hydrolysis of fats. These are esters of palmitic, stearic, and other acids with glycerol. The hydrolysis of such esters yields glycerol and salts of the fatty acids of the esters, called soaps (see page 218). Glycerol may also be made from trichloropropane:

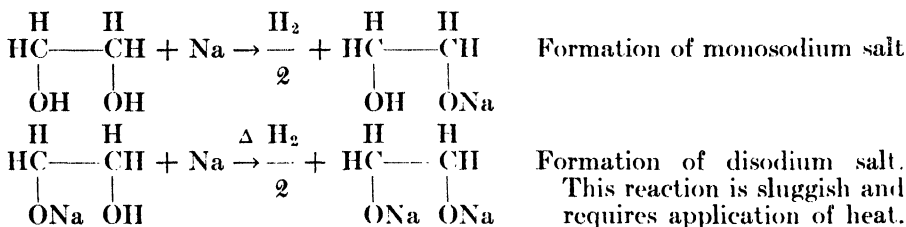


This reaction has practical importance and it helps to prove the structure of glycerol. The trichloropropane is made by reaction of chlorine with allyl chloride, which in its turn is easily made from propylene (page 57), a cheap starting material. For further discussion, see *Ind. Eng. Chem. (News Edition)*, **16**, 326, 632 (1938), *Chem. and Met. Eng.*, **47**, 834 (1940). Glycerol may be made in 25% yield by the fermentation of glucose.

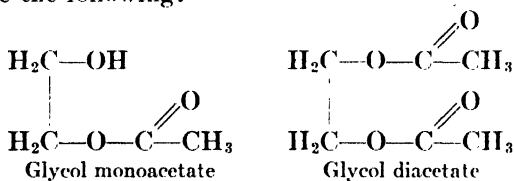
**Diethylene glycol, HOCH<sub>2</sub>CH<sub>2</sub>OCH<sub>2</sub>CH<sub>2</sub>OH,** is a "mixed compound," both an ether and an alcohol. It is soluble in water and in the majority of organic solvents (but not in benzene, or carbon tetrachloride). It is hygroscopic (see glycerol) and an excellent solvent for gums and resins. By nitration, it forms a useful and powerful explosive. Certain of its derivatives have even better solvent powers than the glycol. Its synthesis will be given in the next chapter.

## REACTIONS OF POLYHYDROXY ALCOHOLS

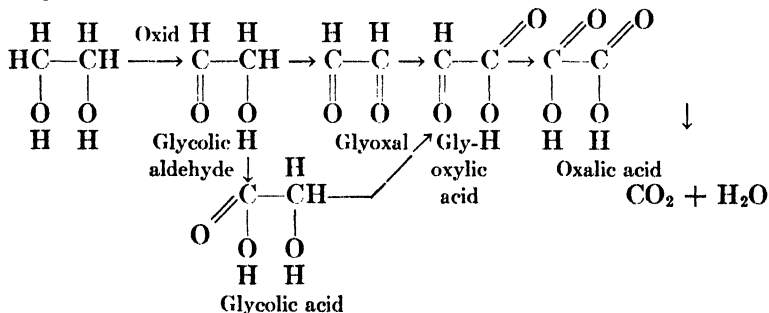
These are the same as have already been shown for the primary, secondary, and tertiary monohydroxy alcohols (any or all of which types may be found within a polyhydroxy alcohol). On account of the fact that either one or more than one of the OH groups may take part in a given reaction, mixed derivatives are often obtained. The equations below bring this out, using ethylene glycol, a di-primary alcohol, as an example.

(1) *Action with sodium:*

(2) *In reactions with acids* one or more OH groups may be affected, giving rise to esters like the following:

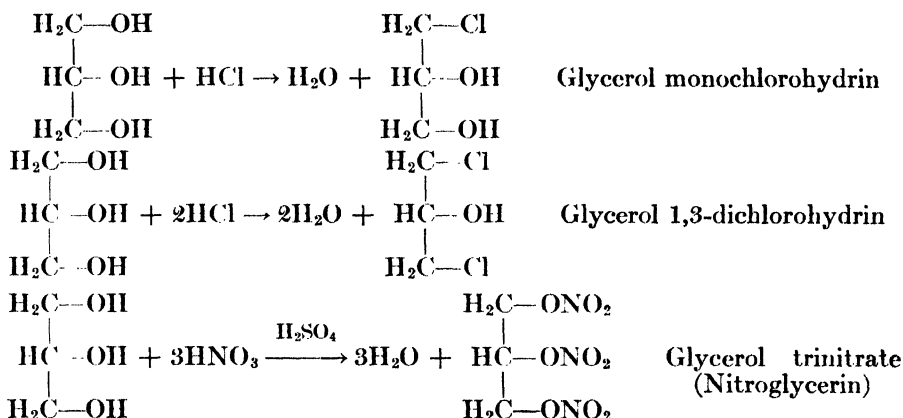


(3) *On oxidation*, a number of intermediate compounds may be formed, depending upon the amount of oxidation borne by each of the carbon atoms. The possibilities in the case of glycol are shown below. All of the substances indicated here are known; however some of them are better made in other ways.



The likeness between the reactions of polyhydroxy alcohols and those of the monohydroxy alcohols already studied is further seen in the following examples applied to glycerol.

(4) *Reaction with inorganic acids* (see esters, page 199):



**Special Reactions of Glycerol.** (1) In making formic acid from oxalic acid, glycerol may be used as a catalyst. The equations are shown on page 175.

(2) Upon dehydration with  $\text{KHSO}_4$ , glycerol loses water to form an unsaturated aldehyde called acrolein. Equations for the reaction are on page 158.

**Sorbitol and Mannitol**,  $\text{CH}_2\text{OH}(\text{CHOH})_4\text{CH}_2\text{OH}$ , are hexahydroxy alcohols which, with dulcitol, are found in nature. Dulcitol is quite sweet, the others less so. They may be prepared by reduction of the corresponding

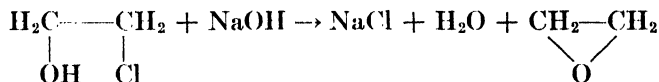
TABLE 10.—DI- AND POLYHYDROXYALCOHOLS

Common name	Official name	M.p., °C.	B.p., °C.	Sp. g., 20°/4°	Ht. of comb.
Glycol.....	1,2-Ethanediol	— 15.6	197.5	1.113 <sup>19</sup>	281.9
1,2-Propylene glycol.....	1,2-Propanediol	.....	189.0	1.038	431
Trimethylene glycol.....	1,3-Propanediol	.....	214 dec.	1.060	
1,4-Dihydroxybutane, Tetra- methylene glycol.....	1,4-Butanediol	+ 16.0	230.0	1.020	
1,5-Dihydroxypentane, Penta- methylene glycol.....	1,5-Pentanediol	.....	239.4	0.994	
1,6-Dihydroxyhexane, Hexa- methylene glycol.....	1,6-Hexanediol	42.0	250.0		
Glycerol.....	1,2,3-Propanetriol	17.9	290.0	1.260	397
1,2,3-Trihydroxybutane.....	1,2,3-Butanetriol	.....	172 <sup>27</sup>	1.232	
Erythritol.....	1,2,3,4-Butanetetraol	126	331	1.451	504.1
Dulcitol.....	1,6-Hexanehexaol	188	295 <sup>3.5</sup>	1.466 <sup>15</sup>	729.1
D-Mannitol.....	.....	166.1	295 <sup>3.5</sup>	1.489	727.6
D-Sorbitol.....	.....	110.0			

hexoses. Mannitol and sorbitol have now become available in large amounts (Atlas Powder Co.), and are recommended for chemical synthesis.

Their nitrates are explosive. Their production involves the electrolytic reduction of glucose.

**Ethylene oxide.** The hydrolysis of ethylene chlorohydrin with mild alkali to form glycol was shown on page 109. When a strong base is used ethylene oxide is produced:



At the same time a certain amount of dioxane is formed. These compounds will be discussed in the next chapter.

### UNSATURATED ALCOHOLS

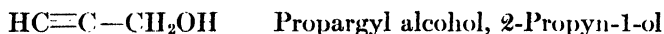
These are hydroxy compounds whose hydrocarbon chain belongs either to the ethylene or the acetylene series.

Examples:

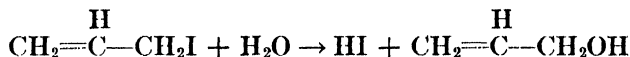
Olefin alcohol,



Acetylene alcohol,

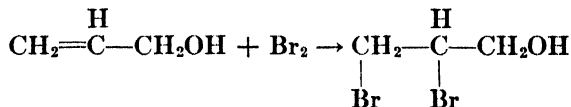


Such compounds may be formed in some instances by general method (1) given for the primary saturated alcohols:

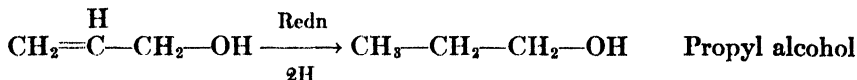


Special methods of preparation are often necessary for their synthesis (see page 250). In their reactions they behave like alcohols and like unsaturated hydrocarbons (see note below). A few type reactions are added to illustrate this point.

(a) *Addition of halogen:*



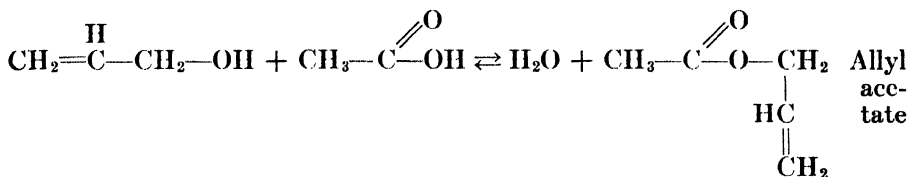
(b) *Reduction:*



\* Vinyl alcohol, the lowest member of the olefin alcohol series, has not been isolated in the alcohol form. See page 145.

Examples (a) and (b) are reactions common to the olefins. Example (c), below, is a reaction of the OH group, common to the alcohols.

(c) *Esterification*:



(d) *Oxidation*. By a choice of conditions oxidation may be confined to the double bond or the primary alcohol. Oxidation of allyl alcohol by dilute potassium permanganate yields glycerol. If the double bond is protected by the temporary addition of bromine, acrolein and acrylic acid may be made.

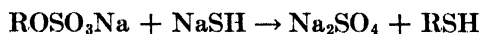
The following has been said before, but may well be repeated for emphasis: when the reactions of a certain group (like the ethylene or acetylene structure, or OH attached to a hydrocarbon radical) have been learned, the information may be put to use to predict the behavior of a new compound in which such groups occur. Thus, in the present instance, one could foretell the reactions shown for allyl alcohol, after a study of ethylene and ethyl alcohol, and their reactions. This is true because the reactions of groups in organic compounds tend to be additive; each group preserves its individual reactions, though the presence of other groups in a molecule at times causes slight alterations.

#### THIOALCOHOLS (THIOLS)

For many organic oxygen compounds we find analogous sulfur derivatives in which sulfur atom takes the place of oxygen. These are frequently called thio-compounds (thio alcohols, thio ethers, thio aldehydes). The sulfur compounds which correspond to the alcohols are commonly called mercaptans, the name arising from the fact that they easily form mercury salts. They are for the most part colorless liquids with a very disagreeable garlic-like odor.

Thioalcohols are prepared by the following **general methods**:

(1) From a metal salt of an alkylsulfuric acid and sodium hydrogen sulfide:

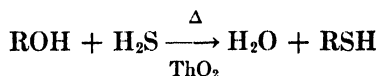


(2) From an alkyl halide and potassium hydrogen sulfide:



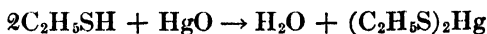
This equation should be compared with the corresponding equation for the preparation of an alcohol, page 96.

(3) From an alcohol and hydrogen sulfide:



#### REACTIONS OF THIOALCOHOLS

(1) *Formation of salts . . . called mercaptides in general:*



The thioalcohols form salts with the heavy metals as well as with the alkali metals and differ in this way from the alcohols. The heavy metal salts are but slightly soluble in water.

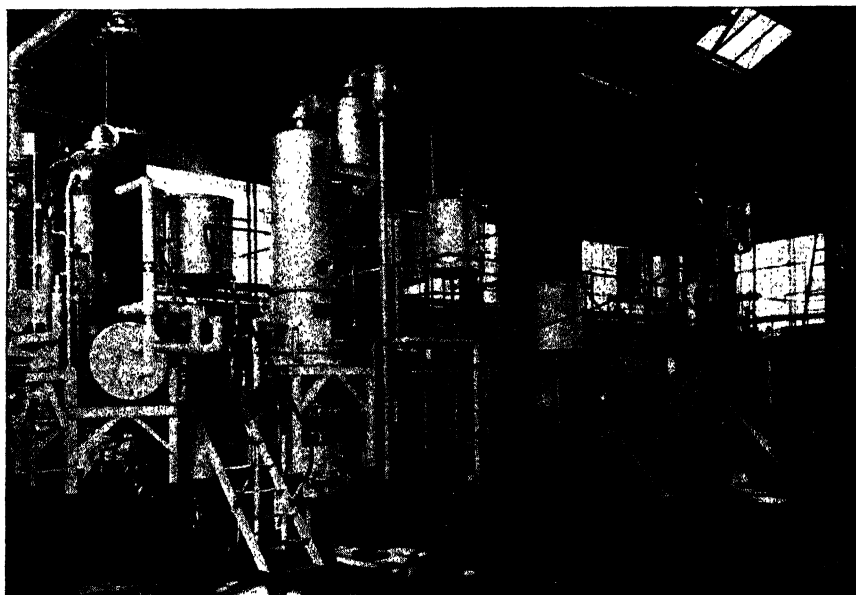
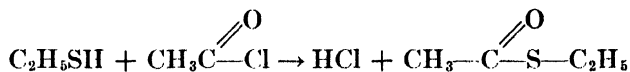
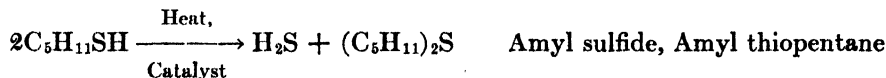


FIG. 24.—Pilot plant for production of glycerol from propylene. (Courtesy of Shell Development Company.)

(2) *Formation of esters.* The formation of ethyl thioacetate is an example:



(3) *Formation of thio ethers or sulfides.* These compounds are further discussed on page 130:



(4) *Oxidation.* Thioalcohols are easily oxidized to dithio compounds (disulfides):



The reverse reaction of reduction is also easily carried out. In the case of glutathione (page 731) this reversible oxidation-reduction reaction is of great importance. Vigorous oxidation gives a sulfonic acid:

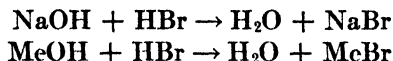


Certain types of petroleum contain organic sulfur compounds including thioalcohols. By the use of sodium plumbite solution (doctor solution) these are changed to disulfides which are less objectionable. The powerful odor of the lower thioalcohols makes them useful as warning agents in mines and in commercial gas lines. A small amount of a thioalcohol is mixed with the gas at a distributing station; if a leak develops the fact is quickly known. It has been found that 0.01 pound of ethanethiol is sufficient for one million cubic feet of natural gas.

#### ELECTRONIC STRUCTURE OF ALCOHOLS

The formula ROH used for an alcohol suggests that of an inorganic base such as sodium hydroxide, and equations for certain of the reactions of alcohols seem to furnish a further analogy between these two classes of hydroxy compounds.

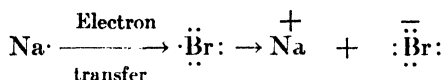
Example:



The apparent analogy disappears when we experiment with these compounds in the laboratory. The neutralization of an acid by a base is an extremely rapid reaction, while the reaction of an alcohol with the acid is quite slow. The solution of base conducts the electric current, but alcohols give solutions which are practically non-conducting; therefore, in the reactions pictured above, the alkyl halide and sodium halide cannot be formed by the same mechanism.

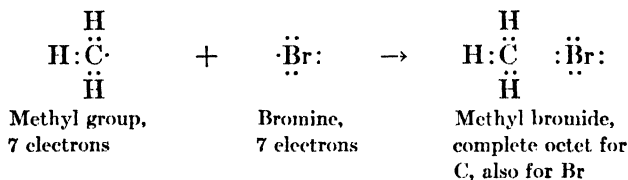
A comparison of sodium bromide and methyl bromide shows that their electronic structures must also be dissimilar. Sodium has one electron in its outer shell (one too many), while bromine has seven (one too few). If now these atoms approach each other and an electron is transferred from sodium to bromine, each atom may satisfy its needs and become a stable ion:



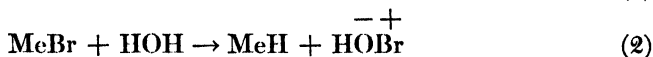
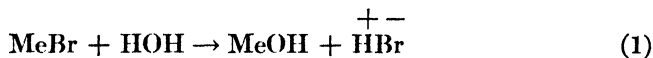


The sodium ion has a positive charge while the bromine is negative (see page 14).

In methyl bromide the methyl group has seven electrons and if it gave an electron to bromine would retain only six. The bromine would be stable but the resulting methyl group would be unstable. Since the two compounds sodium bromide and methyl bromide are different in so many ways, we are convinced that such an electron transfer does not occur, but that the two atoms share a pair of electrons, as is customary in non-polar compounds (see page 14).



The methyl bromide is, however, not absolutely non-polar. When we write the formula we place the shared electrons somewhat closer to the bromine than to the carbon; this because the bromine shows a negative rather than a positive tendency. Thus when we treat the compound with water, reaction (1) below occurs and not (2):



The alcohols too, though they do not ionize freely, either as acids or bases, are not absolutely non-polar compounds. The actual distance of the shared electrons from the carbon in a carbon-oxygen bond probably varies considerably in the different compounds we have considered in this chapter, and in this way we may explain why some alcohols lose hydrogen more easily than others (primary), while others tend to lose hydroxyl in reactions (tertiary).

Certain hydrocarbon groups must be more electronegative than others (hold their bonding electrons more tightly). In the tertiary alcohols several groups are clustered about the carbon holding the oxygen, and evidently the bonding electrons in the C—O bond are farther from carbon than in an isomeric alcohol having a more linear structure. The experimental work which is suggested by these remarks is in progress at this writing, and promises to replace the empirical rules of reaction now in use with much more exact predictions, so soon as the electronegativities are known for more of the groups commonly in use.

## HEATS OF COMBUSTION OF ALCOHOLS

A method (the Kharasch method) has been given for computing the heat of combustion of a saturated hydrocarbon by counting the number of electrons which are shifted when the C—H and C—C unions change to the C—O unions of carbon dioxide, and multiplying by the heat value per mole electron (page 69).

In the alcohols we follow the same scheme for the C—C and C—H bonds. In the case of the C—O bond we have assumed that the bonding electrons are already shifted somewhat toward the oxygen. They therefore suffer a smaller onward shift during the oxidation and give a smaller heat value than electrons in C—C and C—H bonds. For primary alcohols the two electrons of the C—O bond give 13 Kg. cal. per mole during the oxidation; for secondary alcohols the heat value is 6.5 Kg. cal., and for tertiary alcohols the value is 3.5 Kg. cal.

If the total number of electrons for all C—C and C—H bonds is  $N$ , the heat of combustion of a primary alcohol is:

$$H = N \times 26.05 + 13 \text{ Kg. cal. per mole}$$

and for a secondary alcohol is:

$$N \times 26.05 + 6.5 \text{ Kg. cal. per mole.}$$

Values calculated with these formulas agree excellently with the results of experiment and so the original assumptions made above relative to the varying polarity of the alcohols gain in probability.

Examples	Calculated	Recorded
MeOH .....	169.3	170.9
EtOH .....	325.6	327.6
<i>iso</i> PrOH .....	475.4	474.8
<i>tert</i> BuOH .....	628.9	629.3

## REVIEW QUESTIONS

- Write equations for the reactions of ethyl alcohol which show the presence of a hydroxyl group.
- Describe a test by means of which a solid alcohol could be distinguished from a solid paraffin.
- Write equations showing the products which result from the oxidation of propyl alcohol; of isopropyl alcohol.
- Show by equations, the reactions between propyl alcohol and: (a) Sodium; (b) Sulfuric acid; (c) Hydrogen iodide.
- What would be formed by the action of the following reagents upon allyl alcohol: (a) Chlorine; (b) Hydrogen bromide; (c) Dilute potassium permanganate solution?
- What weight of iodine would be absorbed (added) by 5.8 g. of allyl alcohol?
- Give equation; for two reactions of thioalcohols which are not common to the oxygen alcohols.
- Write structural formulas for the isomeric hexyl alcohols. Name each compound, and state whether it is a primary, secondary, or tertiary alcohol.
- What tests could be used to distinguish the following alcohols from each other: (a)  $\text{CH}\equiv\text{C}-\text{CH}_2\text{OH}$  and  $\text{CH}_2=\text{CH}-\text{CH}_2\text{OH}$ ? (b)  $\text{CH}_2=\text{CH}-\text{CH}_2\text{OH}$  and  $\text{CH}_3\cdot\text{CH}_2-\text{CH}_2\text{OH}$ ?
- How could allyl alcohol be made from: (a) Allyl bromide? (b) 3-Bromopropanol-1?

11. What reactions are used to differentiate between primary, secondary, and tertiary alcohols?
12. Prepare a chart or table, showing the sources of methyl, ethyl, propyl, and butyl alcohols.
13. Show by a series of equations how to transform propyl alcohol to:
  - (a) Isopropyl iodide; (b) *n*-Hexane; (c) Propylene.
14. Give a series of facts or arguments supporting the structure of propyl alcohol given in this text.
15. Synthesize ethylene glycol, using ethyl alcohol as a source material, i.e., all organic compounds intermediate in the synthesis must be made from ethyl alcohol.
16. Point out in the glycerol molecule the primary and secondary alcohol groups. Write the formula for a polyalcohol which combines primary and tertiary alcohol groups.
17. Write graphic formulas for the eight amyl alcohols. Name each compound according to the I.U.C. system and write the graphic formula of the first oxidation product of each primary and secondary alcohol of the group.
18. What physical properties distinguish glycols and polyalcohols from monohydroxy compounds?
19. Make a table showing the melting points, boiling points, and densities, respectively, of propane, *n*-propyl alcohol, 1,2-dihydroxypropane, and glycerol. Discuss the change in properties produced by increase in number of OH groups.
20. Review briefly the methods which have so far been given for the production of fuel for automotive machinery.
21. What is the type formula of the monohydroxy saturated alcohols? Of the monohydroxy olefin compounds?
22. Examples were given of the addition of alcohols to inorganic salts to form somewhat stable addition compounds. Give three examples of compounds in which water plays a similar role.
23. If ethyl alcohol is used to produce ethylene, how many liters of ethylene (measured at 25°C. and 730 mm. Hg pressure) could be obtained from 10 moles of alcohol, if the yield in the reaction is to be 80%? How much if the yield is 100% and we use 10 liters of alcohol of 92% strength (density 0.813)?
24. Why is it reasonable that lower monohydroxy alcohols are water-soluble, while those with long chains are not so, but are on the other hand soluble in saturated hydrocarbons?
25. An alcohol of formula  $C_3H_8O$  gives on oxidation the compound  $C_3H_6O$ , then  $C_3H_6O_2$ . What type alcohol is it? Another of formula  $C_3H_8O$  gives upon oxidation  $C_3H_6O$ , then  $CO_2$  and  $H_2O$  and  $C_2H_4O_2$ . What type is it?
26. If you know the boiling point of ethyl alcohol, how can you calculate the approximate boiling point of *n*-butyl alcohol? Make the calculation, then check with the table.
27. Show by a series of equations how to change *n*-butyl alcohol to: (1) *n*-Octane; (2) *sec*-Butyl alcohol; (3) 1-Butene.
28. How could you "predict" that oxidation of 2-hydroxybutane would give butanone-2 and not 2,3-dihydroxybutane?
29. Name two chemical reactions of methyl alcohol different from those of sodium hydroxide.
30. Write equations, using graphic formulas, to show the production of tertiary butyl alcohol from isobutene,  $H_2SO_4$ , etc.
31. It has been shown that alcohols can lose H or OH to form water and at the same time yield new organic compounds. What types of organic compounds are made in this way?
32. Consider the three alcohols represented by these formulas: (a)  $CH_3CH_2CH_2CH_2OH$ ; (b)  $CH_3CHOHCH_2CH_3$ ; (c)  $(CH_3)_3COH$ . Which of these alcohols would be dehydrated most easily? Which would react most readily with: (a) Concentrated HCl; (b) Sodium?
33. Calculate the heat of combustion of *n*-hexyl alcohol; of glycerol; of ethylene glycol.
34. Plot a curve on cross-section paper to show the relationship between the boiling points of normal primary alcohols and the number of carbon atoms in their molecules. On the same paper make a similar curve for the melting points of these compounds vs. the number of carbon atoms. Compare the contours of the two curves obtained.

35. Describe briefly those laboratory tests which you would apply to show that a liquid unknown is an alcohol.
36. Give specific uses for those alcohols which are employed by the physician.
37. What relative weights of methyl alcohol, ethyl alcohol, and ethylene glycol are required to produce the same lowering of the freezing point when added to a given amount of water?
- (R)38.\* A liquid (A) on analysis gives the following figures: combustion of 0.20 g. of the compound yields 0.4757 g. of  $\text{CO}_2$  and 0.2432 g. of  $\text{H}_2\text{O}$ . Its vapor density ( $\text{H}_2 = 1$ ) is 37. Its oxidation yields a monocarboxylic acid, volatile in steam, whose silver salt contains 54.81% silver. What is the structure of (A)? Write the graphic formulas of compounds isomeric with (A) and state what behavior each of these would show when oxidized.
39. How many cc. of concentrated  $\text{HCl}$  solution would be needed to react with all of the salt formed by the action of an excess of sodium upon 25 g. of *n*-propyl alcohol?
- (R)40.† A compound (A) containing C, H, and O was subjected to quantitative analysis. A sample weighing 0.1950 g. gave 0.4290 g.  $\text{CO}_2$  and 0.2340 g.  $\text{H}_2\text{O}$ . The compound was neutral to litmus paper and was unaffected by Fehling solution. Oxidation by one-third mole equivalent of  $\text{K}_2\text{Cr}_2\text{O}_7$  ( $\text{H}_2\text{SO}_4$ ) gave a compound which reduced ammoniacal  $\text{AgNO}_3$  solution. When 10 g. of (A) was treated with sodium, 1867 cc. of hydrogen (N.T.P.) was liberated. What is the probable formula of (A)?

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\* See footnote, page 46.

† In solving problems of this type use the following atomic weight values: H = 1, C = 12, N = 14, O = 16, Na = 23, Cl = 35.5, Br = 80, Ag = 108, I = 127.

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## CHAPTER VI

### ETHERS. THIO ETHERS

Ethers are compounds of the C, H, O group with the type formula  $R-O-R'$ . Reference to the chart on page 805 will show that as the alcohols may be thought of as alkyl derivatives of water, so the ethers are the dialkyl derivatives of water, analogous in their structure to oxides of the metals. The alkyl groups of an ether may be alike (*simple ether*) or different (*mixed ether*).

The aliphatic ethers do not exist in nature, but at least one representative, ethyl ether, has been known since 1540, when according to historical report, this compound was discovered by Valerius Cordus (see table in appendix). The table below gives the constants of several representative ethers, and illustrates at the same time the *system of nomenclature* used for them. It will be noted that the boiling points of the first three simple ethers lie considerably below those of the alcohols from which they are made.

Ethers are isomeric with alcohols, methyl ether with ethyl alcohol, etc. It will be seen that ethers have lower boiling points than their isomeric alcohols.

The most familiar member of the group is ethyl ether, which compound is usually in mind when the term "ether" is employed. Ether is a colorless mobile liquid with a not unpleasant characteristic odor. It is nearly immiscible with water,\* but soluble in the characteristic organic solvents.

Ether is very flammable, burning with a clear yellow flame. With air, ether vapor forms a highly explosive mixture; all laboratory experiments with the compound should for this reason be carried on with caution. Introduced as an anesthetic by Morton in 1846, ether now finds its chief usefulness in this role. The chemist uses ether as a solvent and extracting agent. It readily dissolves fats, resins, oils, and alkaloids, as well as some inorganic substances such as bromine, iodine, and various salts. As ether is but slightly miscible with water, it may be shaken with the latter to remove an oily substance suspended or dissolved in it. The oil will collect in the ether layer above the water, and may thus be isolated upon separation of the upper layer, and subsequent evaporation of the ether. Such a process is termed an *extraction*. Ether is less soluble in a saturated solution of sodium chloride than in water. Therefore, salt may be used in extractions to save ether. This action is termed "salting-out."

\* At 30°C. ether is soluble in water in the proportion of 1 to 19 by weight, and water is soluble in ether in the proportion of 1 to 73.

TABLE 11.—PHYSICAL CONSTANTS OF ETHERS, ETC.

Name		Formula	M.p., °C.	B.p., °C.	Sp. g., 20°/4°
Common	Official				
Methyl ether.....	Methoxymethane	$(\text{CH}_3)_2\text{O}$	-138.5	-23.7	0.661
Methyl ethyl ether.....	Methoxyethane	$\text{CH}_3\text{OC}_2\text{H}_5$	.....	+10.8	0.697
Ethyl ether.....	Ethoxyethane	$\text{C}_2\text{H}_5\text{OC}_2\text{H}_5$	-116.3	34.5	0.708 <sup>25</sup>
Methyl propyl ether.....	Methoxypropane	$\text{CH}_3\text{OC}_3\text{H}_7$	.....	39	0.738
Methyl- <i>n</i> -butyl ether.....	Methoxy- <i>n</i> -butane	$\text{CH}_3\text{OC}_4\text{H}_9$	.....	71	0.744
Ethyl propyl ether.....	Ethoxypropane	$\text{C}_2\text{H}_5\text{OC}_3\text{H}_7$	< -79	62	0.739
Propyl ether.....	Propoxypropane	$\text{C}_3\text{H}_7\text{OC}_3\text{H}_7$	-122	91	0.747
Isopropyl ether.....	.....	.....	-60	68.7	0.725 <sup>21</sup> <sub>0</sub>
Ethyl butyl ether.....	Ethoxybutane	$\text{C}_2\text{H}_5\text{OC}_4\text{H}_9$	.....	91.4	0.752 <sup>20</sup> <sub>20</sub>
Propyl butyl ether.....	Propoxybutane	$\text{C}_3\text{H}_7\text{OC}_4\text{H}_9$	.....	117.1	0.777
Butyl ether.....	Butoxybutane	$\text{C}_4\text{H}_9\text{OC}_4\text{H}_9$	.....	140.9	0.769 <sup>20</sup> <sub>20</sub>
Ethyl hexyl ether.....	Ethoxyhexane	$\text{C}_2\text{H}_5\text{OC}_6\text{H}_{13}$	.....	137.0	.....
Ethylene oxide.....	Epoxyethane	page 127	-111.3	13.5 <sup>747</sup>	0.887 <sup>7°</sup>
Propylene oxide.....	1,2-Epoxypropane	page 127	35	33 <sup>30</sup>	0.859 <sup>0°</sup>
Cellosolve.....	Glycol monoethyl ether	page 128	.....	135.1	0.931 <sup>20</sup> <sub>20</sub>
Methyl cellosolve.....	Glycol monomethyl ether	.....	.....	125.0	0.966 <sup>20</sup> <sub>20</sub>
Butyl cellosolve.....	Glycol monobutyl ether	.....	.....	170.6	0.902 <sup>20</sup> <sub>20</sub>
Carbitol.....	.....	page 128	.....	201.9	0.99 <sup>20</sup> <sub>20</sub>
Diethylene glycol.....	<i>bis</i> (2-hydroxyethyl) ether	page 128	.....	244.8	1.12 <sup>20</sup> <sub>20</sub>
Dioxane.....	1,4-Dioxane	page 128	.....	101.1	.....
Dichlorodiethyl ether.....	<i>bis</i> (2-chloroethyl) ether	page 129	.....	178	1.213 <sup>20</sup> <sub>20</sub>
Vinyl ether.....	.....	page 130	.....	39	.....
Diethyl sulfide.....	Ethylthioethane	page 130	-99.5	92	0.837
Allyl sulfide.....	.....	page 131	-83	138.6	0.888 <sup>26-8°</sup>
Mustard gas.....	<i>bis</i> (2-chloroethyl) sulfide	page 132	.....	.....	.....

Several other ethers, notably isopropyl ether, are used as solvents. Isopropyl ether is often used in place of ethyl ether for extraction in the laboratory. It is a little more effective as an extracting agent, and on account of its higher boiling point is not quite so dangerous as ethyl ether.\*

Whitmore calls attention to the value of methyl ether as a solvent, also as a refrigerant in the "quick freezing" of foods. Foods may be exposed directly to it during refrigeration without acquiring objectionable taste or odor.

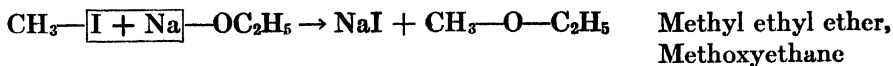
\* Ethers, such as isopropyl ether, are very suitable for blending with gasoline to give fuel of high octane rating.

## PREPARATION OF ETHERS

(1) Method of Williamson (1851) by reaction of an alkyl halide and an alkoxide. Both simple and mixed ethers may be prepared by this method.

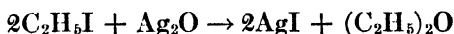


Ethoxyethane



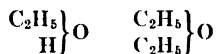
Note the apparent similarity of this reaction to the Wurtz synthesis, page 81. A modification of this reaction, used to make mixed ethers, is shown on page 574.

(2) Preparation from an alkyl halide and silver oxide. Only simple ethers may be made in this way; the method is not practical.



The Williamson synthesis (1) and synthesis (2) establish without question the constitution of the ethers, and prove that in these compounds the alkyl groups are directly connected to the oxygen atom.

The Williamson synthesis of ether was important in the development of chemical theory. In 1850 the formula for water was HO, for alcohol,  $\text{C}_4\text{H}_5\text{O}$ , HO and for ether,  $\text{C}_4\text{H}_5\text{O}$  ( $\text{C} = 6$ ,  $\text{O} = 8$ ). Ether was thought by most chemists to be alcohol less one molecule of water. However Gerhardt and Laurent adopted the view that alcohol and ether were substitution products of water formulated as follows:



Williamson's experiment in which he made methyl ethyl ether from interaction of potassium ethoxide and methyl iodide and *also* from *potassium methoxide and ethyl iodide* showed conclusively that the Laurent-Gerhardt hypothesis was the correct one. It followed that ether must have two hydrocarbon radicals, not one, and that the formula for water must be  $\text{H}_2\text{O}$ .

(3) Preparation by dehydration of an alcohol. With ethanol and other lower primary alcohols this dehydration may be effected by passing the vapor of the alcohol over alumina heated to  $250\text{--}260^\circ$ . In the laboratory and in commercial practice sulfuric acid is generally used as a "water-remover."

Equal molecular proportions of ethyl alcohol and sulfuric acid are first allowed to react. An alkylsulfuric acid is formed as shown on page 53. This then reacts with additional alcohol to produce the ether:



The sulfuric acid is regenerated and may now act on a further supply of alcohol. For this reason this process of making ether is called the "continuous etherification process." Theoretically a single charge of sulfuric



acid should catalytically transform an unlimited amount of alcohol to ether, but actually the acid must be renewed after a time because some of it is reduced by side-reactions. It is desirable to lower the temperature of the etherification reaction, since ethyl hydrogen sulfate may decompose to produce ethylene and sulfuric acid (page 53). Aluminum sulfate is used as a catalyst to allow the reaction to proceed at 120–140°; above 145° the ethylene reaction would supervene. The proportions of acid and alcohol used (excess of alcohol) are also unfavorable for the production of ethylene.

If we heat the ester of a primary alcohol and benzenesulfonic acid (page 439) with an excess of alcohol, an ether is produced without the undesirable charring which always takes place with the use of sulfuric acid.

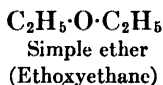
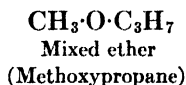
If an alkylsulfuric acid is caused to react with another alcohol than the one first employed, a mixed ether results.

Ether as prepared by this process contains water, alcohol, and sulfurous acid as impurities. The acid and a large part of the alcohol may be removed by shaking with sodium hydroxide solution. Remaining alcohol and much of the water are taken out by treatment with strong calcium chloride solution. By introduction of sodium in the form of wire or thin shavings, or by the use of  $P_2O_5$  one removes the last traces of water. Such treatment is necessary if the ether is to be used for a Wurtz or a Grignard reaction.

The sulfuric acid method serves for lower members of the ether series with normal chains. The higher alcohols and branched-chain members give undesirable amounts of olefinic compounds when heated with sulfuric acid. Isopropyl ether is secured as a by-product of the synthesis of isopropyl alcohol from propylene. On account of the tremendous volume of gasoline made by cracking, about 400,000,000 or more gallons of this ether are available annually.

**Metamerism.** A mixed ether may be isomeric with a simple ether as in the examples given here. Such isomers are called *metamers*. They occur in the series of ethers, amines, etc.

Examples:

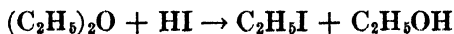


### REACTIONS OF ETHERS

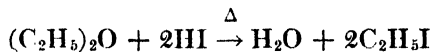
The ethers are rather inert. This would be expected because they do not possess hydroxyl groups or multiple bonds. Their structure resembles that of the saturated hydrocarbons.

(1) *Oxidation.* This reaction gives the same products from an ether as would be formed from the alcohols from which the ether was prepared.

(2) *Reaction with hydrogen iodide.* Hydrogen iodide in the cold yields alkyl halide and alcohol:



When this mixture is heated with an excess of hydrogen iodide, the alcohol is converted to alkyl halide:

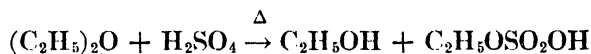


(3) When an ether is boiled with water and acid for some time, hydrolysis occurs with the production of alcohols:



Bases do not catalyze this hydrolysis.

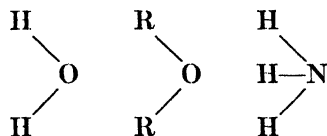
(4) Ethers are soluble in cold concentrated sulfuric acid. On addition of water to such a solution, the ether is recovered unchanged. However, if the solution is heated an ester of sulfuric acid is formed:



(5) *Reaction with halogens.* An ether would be expected to react with chlorine and bromine because the saturated hydrocarbons do so. Halogen tends to substitute first on the *alpha* carbon, that is the one next to the oxygen. The *beta* chlorinated ether mentioned later is not made by direct chlorination.

#### ELECTRONIC STRUCTURE OF ETHER. OXONIUM SALTS

The formulas for water, ammonia, and ether are quite similar. In each we have oxygen or nitrogen united to hydrogen or a hydrocarbon radical:



The likeness between ether and ammonia is even more apparent in the electronic formulas:

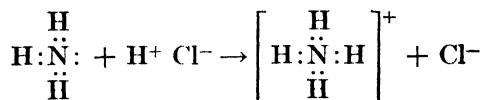


In each case the nuclear atom, though possessed of the full quota of groups or atoms called for by its valence, is yet capable of holding additional atoms or groups. These compounds are thus in a sense unsaturated. The unshared electrons are called "lone pairs."

Certain reactions of addition have long been known for these compounds and are well explained by the electronic formulas. Consider the reaction of ammonia with an acid:



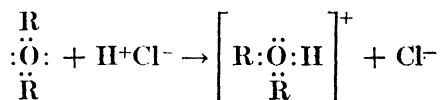
If the proton of the acid joins to the nitrogen of ammonia all of the valence electrons of the nitrogen will be used, and at the same time the  $\text{NH}_4$  group will acquire a positive charge:



We now have the ions  $\text{NH}_4^+$  and  $\text{Cl}^-$ .

Ether dissolves freely in sulfuric acid and in concentrated hydrochloric acid and forms addition compounds with many substances, both organic and inorganic. There is hardly a doubt that many if not all of such compounds are formed as shown above.\*

Example:



Since the addition complexes of ammonia are known as ammonium salts, the name **oxonium salts** has been adopted for the compounds similarly formed by ether and other similar oxygen compounds. In the Grignard reaction (page 570) very practical use is made of the ability of ether to form oxonium salts.

When ether is exposed to air for some time it acquires a somewhat pungent odor and is found to have taken on the properties of an oxidizing agent. Distillation of such ether has frequently resulted in explosions which have been traced to the presence of peroxide compounds. Possibly such compounds are formed by addition of oxygen or perhaps of hydrogen peroxide by the unused electrons of the oxygen atom of the ether; they may also be true oxidation products. The presence of these peroxides makes ether unfit for use as an anesthetic.

#### Digression. Association of Water, Alcohols, and Related Compounds.

It must seem surprising to the thoughtful student that a substance of such low molecular weight as water should have a boiling point higher than that of heptane, whose molecular weight is 100. Another surprise comes with a comparison of the boiling points of saturated hydrocarbons and alcohols:

	B.p.		B.p.
$\text{C}_4\text{H}_{10}$ .....	-0.5°C.	$\text{C}_4\text{H}_9\text{OH}$ .....	117.0°C.
$\text{C}_6\text{H}_{12}$ .....	36.0	$\text{C}_6\text{H}_{11}\text{OH}$ .....	137.9

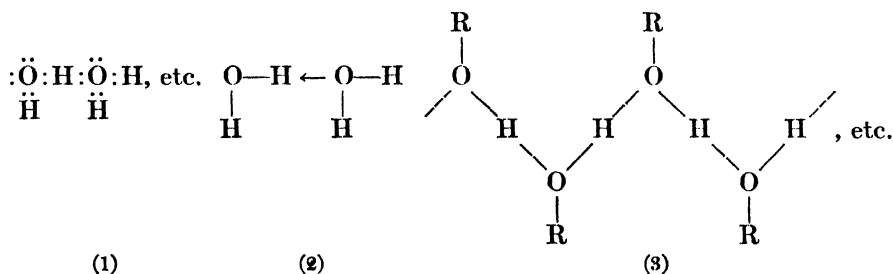
Here we note that the simple substitution of OH for H of the hydrocarbon

\* In this reaction ether shows the properties of a weak base just as ammonia does in its reaction with HCl. Any substance which, like ether or ammonia, can take protons from an acid, is defined as a base. For a conflicting theory see *J. Am. Chem. Soc.*, **60**, 2528 (1938).

raises the boiling point about  $100^{\circ}$ . The explanation lies in the fact that water and the alcohols are associated compounds. Like the ethers they form addition compounds, in this case adding to themselves.

The compounds really have molecular weights larger than illustrated by their simple formulas. Thus liquid water consists of  $\text{H}_2\text{O}$ ,  $(\text{H}_2\text{O})_2$ ,  $(\text{H}_2\text{O})_3$ , mixed in varying proportions. The ethers, which are not associated compounds, have boiling points much lower than those of the alcohols. Their boiling points are to be considered as "normal" while the boiling points of alcohols are abnormally high.

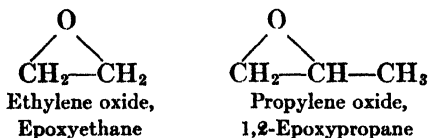
In the association of water molecules the hydrogen atom of one molecule acquires an effective valence of two units. This is possible by virtue of the fact that the oxygen atom of water has valence electrons which are not employed (see page 13). A new type of bond, the **coördinate bond** exists between the oxygen and hydrogen. In this type of bond two electrons are shared as usual, but *both of them come from one atom* (the donor atom). In a normal covalent bond each atom contributes one electron. The arrow in the second formula points from donor to acceptor atom.



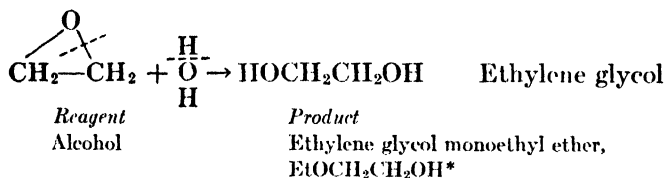
Alcohol molecules associate in a similar way (see (3) above). This special type of union is known as a **hydrogen bridge** or **hydrogen bond**. The hydrogen atom of the bridge is not actually in possession of four electrons as shown in (1); really this hydrogen tends to be alternately bonded to each of the two oxygen atoms. A true formula, if it could be drawn, would show the valence rapidly alternating from one position to the other (see Resonance, page 398).

#### ALKYLENE OXIDES, HALOGENATED ETHERS, ETC.

The ethers so far discussed have all possessed two hydrocarbon groups. It is, however, possible to form an ether-like compound with but one hydrocarbon chain, two carbons of the chain being linked through oxygen as well as directly. Examples of such cyclic ethers are:



**Ethylene oxide** is obtained by heating ethylene chlorohydrin with alkali (page 112). It is a colorless gas (b.p., 10.7°C.) soluble in water, alcohol, and ether. It is used as a fumigating agent and in synthetic work. Its great value in synthesis depends upon the fact that the oxygen bridge is easily opened, and by treatment with unsymmetrical reagents a molecule is obtained with different functions at either end. Such bifunctional compounds are usually valuable. The number of such compounds obtainable from ethylene and propylene oxides and like compounds is very large and only a few examples will be given here. Some others will appear later. The reaction will be indicated in the first instance, and thereafter only the reagent and final product will be shown, as the mode of reaction is in all cases identical with that shown.



This product, known as "Cellosolve" is a solvent for cellulose nitrate and useful in many other roles. Methyl and butyl alcohols give methyl and butyl cellosolves. These are good solvents, especially for making lacquers. They are miscible with water.

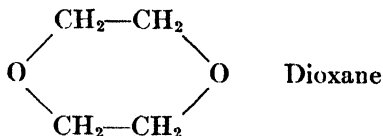
Ethylene glycol.....  $\text{HIOCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OH}$ , Diethylene glycol.

This compound is discussed on page 109.

Cellosolve.....  $\text{EtOCH}_2\text{CH}_2\text{OCH}_2\text{CH}_2\text{OH}$ , Diethylene glycol monoethyl ether

This compound is known as "Carbitol." It has been used as a plasticizer and as a solvent for cellulose nitrate. Methyl and butyl cellosolves give methyl and butyl carbitols, valuable solvents. They are water-soluble.

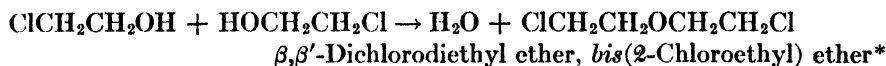
**Dioxane, 1,4-Dioxane, Diethylene oxide**, a by-product in the formation of ethylene oxide, is a cyclic ether of a special type:



It is made from ethylene glycol by distillation with concentrated sulfuric acid in small amount. It is a good solvent and especially interesting because it is water-soluble. As would be predicted it forms oxonium compounds, that with sulfuric acid being a stable compound with melting point of 101°C.

\* For significance of the abbreviation, see footnote, page 94.

**Dichlorodiethyl ether.** When ethylene chlorohydrin is treated with concentrated sulfuric acid at 100°, ether formation occurs:



The product, dichlorodiethyl ether, is an excellent solvent for oils, fats, gums, and waxes. Its high specific gravity, low water solubility, and relatively



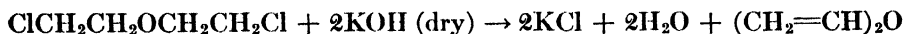
FIG. 25.—Portion of Robert Hinckley painting of first operation under ether at Massachusetts General Hospital. (*Boston Medical Library.*)

high boiling point make it a good extracting agent. It has been mentioned in connection with the “chlorex” extraction process for lubricating oil refining.

Treatment of dichlorodiethyl ether with ammonia yields morpholine (page 316).

\* The use of *bis* in a name signifies that two identical groups are joined to a given atom.

**Vinyl ether, Divinyl ether,  $(\text{CH}_2=\text{CH})_2\text{O}$ ,** is an example of an unsaturated ether.\* The compound is made from dichlorodiethyl ether by treatment with alkali:



The compound has a boiling point very near that of ethyl ether. It has been tried as an anesthetic and found to be more rapid than ether both in onset of anesthesia and recovery therefrom. Note the chemical likeness to both ethylene and ether.

### THIO ETHERS OR ALKYL SULFIDES

Thio ethers, compounds analogous to ethers, in which sulfur atom takes the place of oxygen, are, like ethers, colorless liquids insoluble in water, but soluble in alcohol, ether, and other organic solvents. Their odors are likely to be disagreeable as ordinarily prepared, but the pure compounds are not unpleasant.

The *type formula* for this series is  $\text{R}-\text{S}-\text{R}'$ , and as with the oxygen ethers, both simple and mixed derivatives are possible.

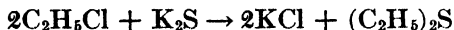
Simple:  $\text{C}_2\text{H}_5-\text{S}-\text{C}_2\text{H}_5$   
Ethyl sulfide, Ethyl-  
thioethane

Mixed:  $\text{CH}_3-\text{S}-\text{C}_3\text{H}_7$   
Methylthiopropene

It will be seen that the above compounds are metamers. Metamerism exists in this series as with the ethers, etc.

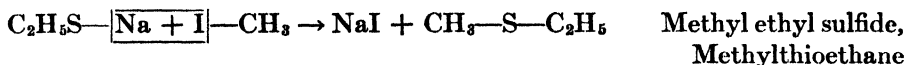
### PREPARATION OF THIO ETHERS

(1) Action of an alkyl halide with a metallic sulfide:



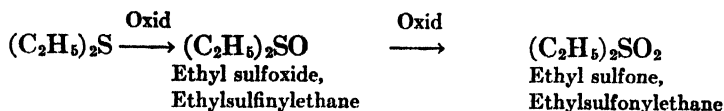
This reaction should be compared with reaction (2) for the preparation of oxygen ethers.

(2) By a variant of the Williamson reaction.



### REACTIONS OF SULFIDES

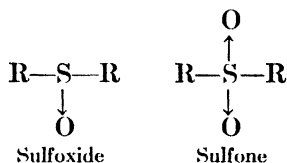
(1) *Oxidation.* Compounds called sulfoxides and sulfones are obtained upon oxidation of the organic sulfides. Nitric acid is used to obtain sulfoxides; by use of concentrated nitric acid or potassium permanganate sulfones are made.



\* This is sold under the name Vinethene.

The preparation of several sulfones of importance in medicine is shown on page 155.

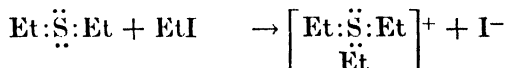
The sulfoxides are interesting examples of compounds possessing a coördinate bond. The sulfur atom holding two pairs of unshared electrons is able to donate a pair to an oxygen atom. The oxygen, which has but six valence electrons, thus acquires a normal octet. Sulfur is the donor, oxygen the acceptor (see page 127). In a sulfone molecule there are two coördinate links.



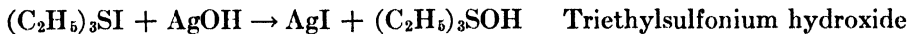
(2) *Addition of alkyl halides to form sulfonium compounds:*



Thioethers show additive powers as do their oxygen analogs, which is to be expected in view of the chemical similarity of oxygen and sulfur. The electronic formulation for the reaction shown above is:



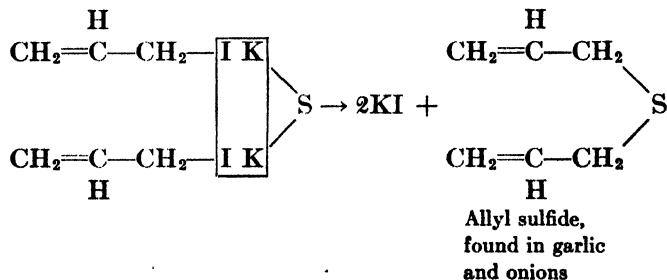
During the reaction the iodine takes possession of its full quota of eight electrons and leaves the ethyl group a positive ion. After the ethyl group joins the sulfur this positive charge belongs to the complex. The compound is a salt. Upon treatment with silver hydroxide there is an exchange of ions to form the sulfonium base, triethylsulfonium hydroxide.



Bases such as this are as strong as sodium hydroxide.

#### UNSATURATED AND HALOGENATED THIO ETHERS

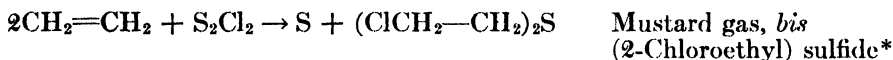
The structure of allyl sulfide is shown below as an illustration of an unsaturated compound.





**Mustard Gas.** The formation of "Mustard Gas,"  $\beta,\beta'$ -dichlorodiethyl sulfide is shown below. This substance was one of the highly important war gases in World War I. It appears to penetrate the skin very rapidly, and after some delay causes first intense irritation, then blistering and finally necrosis. It may be absorbed through the lungs; injury to the heart and internal organs follows if any reaches the blood stream. The strong vesicant action is not well understood.

By chlorination of mustard gas non-vesicant products result. The products of light oxidation are also non-vesicant. These means are thus available if the compound is to be destroyed. The overall reaction for its preparation is:



Other substances used as war gases are shown on pages 323, 606.

### REVIEW QUESTIONS

- What ether would be formed by the interaction of:
  - Sodium methoxide and methyl iodide?
  - Sodium methoxide and propyl iodide?
  - Sodium ethoxide and methyl iodide?
  - Sodium propoxide and methyl iodide?
- Write equations for the action of silver oxide upon the following alkyl halides:
  - Methyl iodide; (b) Ethyl iodide; (c) Propyl iodide; (d) Isopropyl iodide.
- What ethers would be formed by the reaction of ethylsulfuric acid (ethyl hydrogen sulfate) and propyl alcohol?
- What products are formed when a mixture of hydrogen iodide and methyl propyl ether is heated?
- Write equations showing how the following ethers would react with cold HI solution and with hot HI solution in excess.
  - Methyl propyl ether; (b) Ethyl isopropyl ether; (c) Butyl ether.
- How could a mixture of ether and *n*-pentane be separated?
- A certain ether has the formula  $\text{C}_4\text{H}_{10}\text{O}$ . Describe the steps which would be necessary to determine its structure.
- Write graphic formulas for ethers of molecular formula  $\text{C}_4\text{H}_{10}\text{O}$ . Write an equation for the preparation of each compound.
- Write equations showing what compound would be produced by the interaction of dimethyl sulfide and methyl iodide. Show by an equation the action of silver hydroxide upon this compound.
- In what respects do thio ethers differ from oxygen ethers?
- Give equations for two methods of making ethyl ether from ethyl alcohol.
- Write structures for the ethers and alcohols having the formula  $\text{C}_4\text{H}_{10}\text{O}$ . Which compound of this group should have the highest boiling point?
- What are oxonium compounds? What elements besides oxygen and nitrogen should form compounds of this type?
- How could you prove the absence of OH group in an ether?
- What class of organic compounds is isomeric with the ethers? What type formula is common to these compounds? What reagent will react with compounds of either class?

\* See footnote, page 129.

16. What test would distinguish an ether from a saturated hydrocarbon? Describe it.
17. In connection with the first use of ether for anesthesia the names of Long, Morton, and Simpson are cited. Consult an encyclopedia to learn what contribution was made by each of these.
18. What compounds might be formed by reaction of ammonia and ethylene oxide?
19. What compound should form by treatment of ethyl ether with anhydrous hydrogen chloride in large excess? Show its electronic structure.
20. What objection might there be to the use of the sulfuric acid method for making ethers from secondary or tertiary alcohols?
21. Why would ether be "expected to react" with chlorine or bromine?
22. Write equations for the formation of methyl and butyl cellosolves and for methyl and butyl carbitols.
23. Why should cellosolve be a more versatile solvent than ether or alcohol?
24. By what tests is an ether to be distinguished from a saturated monohydroxy alcohol?
25. Describe how one would determine the nature of the alkyl groups of an ether of formula  $C_6H_{12}O$ .
26. When making ether by the sulfuric acid method ethylene may be formed. How can one lower the ethylene yield?
- (R)27. Tell how to separate by chemical methods a mixture of acetic acid, acetone, and ethyl ether.
28. Define and illustrate the term "metamerism."
- 29.\* A compound (A) contains 64.88% C, 13.51% H, and 21.62% O. Its vapor density ( $H_2 = 1$ ) is 37. When it is heated with an excess of HI solution two alkyl iodides are formed, containing respectively 89.45% and 74.71% iodine. Indicate possible structures for the compound (A). What further work is necessary in order to fix the structure of the compound?
- (R)30. Analysis of the compound (A) yields the following results: combustion of a sample weighing 0.1680 g. yields 0.3695 g.  $CO_2$  and 0.2015 g.  $H_2O$ . The vapor density of (A) is 30. When treated with concentrated sulfuric acid it is converted in part to an olefin (B) containing 85.71% C. Addition of HBr to this olefin yields an alkyl halide (C) containing 65.04% Br. The compound (C) reacts with sodium propoxide to yield a compound with a vapor density of  $50 \pm 1$ . Final tests to prove the structure of (A) included oxidation which gave a monocarboxylic acid (D) whose silver salt contained 59.66% Ag. Explain the reactions discussed above, and show graphic formulas for (A), (B), (C), and (D).

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2. COTTON AND ROARK. Ethylene oxide as a fumigant. *Ind. Eng. Chem.*, **20**, 805 (1928).
3. RUSS. Fumigation with ethylene oxide. *Ind. Eng. Chem.*, **22**, 328 (1930).
4. HUGGINS. Hydrogen bridges in organic compounds. *J. Org. Chem.*, **1**, 407 (1936).
5. BROWNE. Emerson and chemistry. *J. Chem. Education*, **5**, 275 (1928).

\* See footnote, page 119.

## CHAPTER VII

### ALDEHYDES AND KETONES

Aldehydes and ketones are highly important compounds of the C, H, O group, which, because of certain similarities in structure and reactions, may well be studied side by side. Both aldehydes and ketones are oxidation products of the alcohols, the former being produced by the oxidation of primary alcohols, whereas ketones form when secondary alcohols are oxidized.

The *type formula* for an aldehyde is  $\text{R}-\overset{\text{H}}{\underset{\text{R}}{\text{C}}}=\text{O}$ ; that for a ketone is  $\text{R}-\overset{\text{H}}{\text{C}}=\text{O}$ . Both contain carbon united to oxygen by two bonds (the *carbonyl group*). Aldehydes differ from ketones in that they contain the carbonyl group united to hydrogen and an alkyl group; in ketones two alkyl groups are attached to carbonyl. A number of the reactions of aldehydes and ketones depend on the unsaturated  $\text{C}=\text{O}$  group, which takes part in additions similar in some respects to those already noted in the case of ethylene and its congeners.

**Nomenclature.** Aldehydes on oxidation yield acids with the same number of carbon atoms, and are commonly named after these acids.

Examples of common names:

$\text{HC}=\overset{\text{H}}{\text{O}}$       Formaldehyde; oxidizes to formic acid.      Name condensed from "Formic aldehyde."

$\text{CH}_3\text{C}=\overset{\text{H}}{\text{O}}$       Acetaldehyde; oxidizes to acetic acid.      Name condensed from "Acetic aldehyde."

Also, they are named by a system similar to that used for the alcohols, i.e., from the saturated hydrocarbon with like number of carbon atoms, with names ending in *al*.

Examples of I.U.C. names:

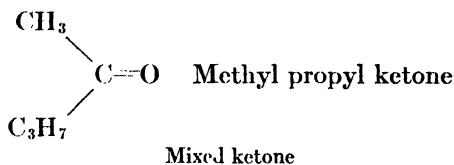
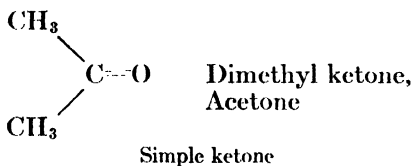
$\text{CH}_3\text{C}=\overset{\text{H}}{\text{O}}$       Ethanal

$\text{C}_3\text{H}_7\text{C}=\overset{\text{H}}{\text{O}}$       Butanal

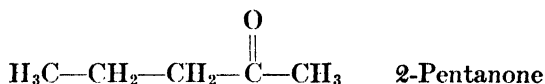
To save space the aldehyde group is usually printed as CHO; thus ethanal would be printed  $\text{CH}_3\text{CHO}$ .

Ketones are named as are the ethers (page 122) i.e., by the word "ketone" preceded by the names of the alkyl groups attached to carbonyl.

Examples:



Ketones are frequently named by the I.U.C. system. The names are taken from the saturated hydrocarbons with like carbon content, using names ending in "one" (pronounced "own"), and a number to indicate the position of the C=O group in the chain. The example below will indicate the use of this system:



The above formula takes less space when printed as  $\text{CH}_3\text{CH}_2\text{CH}_2\text{COCH}_3$ ; therefore the formulas for ketones are often shown in the condensed style. Both simple and mixed ketones are known, an example of each type being illustrated above. The formulas and some of the physical properties of aldehydes and ketones are shown in Tables 12 and 13.

TABLE 12.—CONSTANTS OF ALDEHYDES

Name	Formula	M.p., °C.	B.p., °C.	Sp. g., 20°/4°	Ht. of comb.
Formaldehyde.....	HCHO	— 92.0	— 21.0	0.815 <sup>-20</sup>	134
Acetaldehyde.....	$\text{CH}_3\text{CHO}$	— 123.5	+ 20.2	0.783 <sup>18</sup>	279
Propionaldehyde.....	$\text{C}_2\text{H}_5\text{CHO}$	— 81.0	49.5 <sup>740</sup>	0.807	434
<i>n</i> -Butyraldehyde.....	$\text{C}_3\text{H}_7\text{CHO}$	— 99.0	75.7	0.817	
Isobutyraldehyde.....		— 65.9	63.0 <sup>757</sup>	0.794	597
Valeraldehyde.....	$\text{C}_4\text{H}_9\text{CHO}$	— 91.5	103.4	0.819 <sup>11</sup>	
Isovaleraldehyde.....		— 51.0	92.5	0.803 <sup>17</sup>	
Trimethylacetaldehyde...		+ 3.0	75.0	0.793 <sup>17</sup>	
<i>n</i> -Caproic aldehyde.....	$\text{C}_5\text{H}_{11}\text{CHO}$	.....	130.0	0.819 <sup>15/16</sup>	
Heptaldehyde.....	$\text{C}_6\text{H}_{13}\text{CHO}$	— 42.0	155	0.817	1062.4
<i>n</i> -Caprylic aldehyde.....	$\text{C}_7\text{H}_{15}\text{CHO}$	.....	167–70	0.821	
Acrylic aldehyde.....	$\text{CH}_2=\text{CHCHO}$	— 87.7	52.5	0.841	390
Crotonaldehyde.....	$\text{CH}_3\text{CH}=\text{CHCHO}$	— 69.0	102.2	0.859 <sup>14</sup>	542
Propargyl aldehyde.....	$\text{HC}\equiv\text{CCHO}$	.....	60.0		

### PHYSICAL PROPERTIES OF ALDEHYDES AND KETONES

Although these two classes of compounds have many points of similarity in their chemical properties, their first members, at least, are physically

quite different. Formaldehyde, the first of the aldehyde series, is a gas, while acetaldehyde boils at 20.2°. Further members of this series (up to the compound with 12 carbon atoms) are colorless liquids. Formaldehyde and acetaldehyde have particularly disagreeable and irritating odors, but the higher liquid aldehydes have a pleasant odor. Many are found in flower oils.

TABLE 13.—CONSTANTS OF KETONES

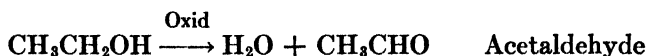
Names of radicals	Formula	M.p., °C.	B.p., °C.	Sp. g., 20°/4°	Ht. of comb.
Dimethyl.....	CH <sub>3</sub> COCH <sub>3</sub>	−94.6	56.5	0.792	427
Methyl ethyl.....	CH <sub>3</sub> COC <sub>2</sub> H <sub>5</sub>	−85.9	79.6	0.805	582
Diethyl.....	C <sub>2</sub> H <sub>5</sub> COC <sub>2</sub> H <sub>5</sub>	−42.0	102.7	0.816 <sup>19°</sup>	736
Methyl propyl.....	CH <sub>3</sub> COC <sub>3</sub> H <sub>7</sub>	−77.8	101.7	0.812 <sup>15°/16°</sup>	736
Methyl isopropyl.....	.....	−92.0	95.0	0.803	734
Methyl <i>n</i> -butyl.....	CH <sub>3</sub> COC <sub>4</sub> H <sub>9</sub>	−56.9	127.5	0.830 <sup>11°</sup>	895
Methyl isobutyl.....	.....	−84.7	118.0	0.803	
Methyl <i>sec</i> -butyl.....	.....	.....	117.8	0.815 <sup>16°</sup>	
Ethyl propyl.....	C <sub>2</sub> H <sub>5</sub> COC <sub>3</sub> H <sub>7</sub>	.....	124.0	0.813	
Ethyl isopropyl.....	.....	.....	114.0	0.814 <sup>18°</sup>	
Dipropyl.....	C <sub>3</sub> H <sub>7</sub> COC <sub>3</sub> H <sub>7</sub>	−32.6	143.5	0.821	1051
Methyl amyl.....	CH <sub>3</sub> COC <sub>5</sub> H <sub>11</sub>	.....	150.0	0.822	
Dibutyl.....	C <sub>4</sub> H <sub>9</sub> COC <sub>4</sub> H <sub>9</sub>	−5.9	188–92	0.827 <sup>13°</sup>	
Diamyl.....	C <sub>5</sub> H <sub>11</sub> COC <sub>5</sub> H <sub>11</sub>	+14.6	226.3	0.826	
Diethyl.....	C <sub>6</sub> H <sub>13</sub> COC <sub>6</sub> H <sub>13</sub>	33.0	264.0	0.825 <sup>30°</sup>	
Diheptyl.....	C <sub>7</sub> H <sub>15</sub> COC <sub>7</sub> H <sub>15</sub>	39.0	178		

Ketones are colorless liquids (up to (C<sub>6</sub>H<sub>13</sub>)<sub>2</sub>C=O), with an ethereal, pleasant odor. Higher members of both series are colorless solids, practically odorless. Only the first few members of the aldehyde and ketone series are freely water-soluble.

### PREPARATION OF ALDEHYDES

The importance of the aldehydes for the synthetic work of the organic chemist has led to the perfection of many methods for the production of these compounds, of which the following are the more generally applicable.

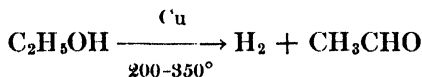
(1) Aldehydes are formed by the oxidation of primary alcohols. Thus ethyl alcohol on oxidation yields acetaldehyde:



A dichromate with sulfuric acid is usually employed when this reaction is carried out in the laboratory. Since an aldehyde is more easily oxidized than the alcohol from which it is being formed, steps must be taken to remove it promptly from the oxidizing mixture, and so prevent its oxidation to acid. Aldehydes have lower boiling points than the corresponding

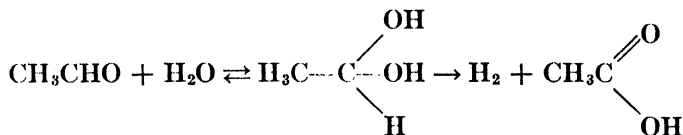
alcohols and so tend to escape from the hot oxidizing mixture. In preparing acetaldehyde and propionaldehyde the escape of the aldehyde is assisted by blowing a current of inert gas through the mixture.

(2) An aldehyde may be formed by passing the vapor of a primary alcohol over hot copper:



This reaction shows the derivation of the name aldehyde (from *alcohol dehydrogenatum*), that is, alcohol less hydrogen. Some of the acetaldehyde of commerce is made by this process.

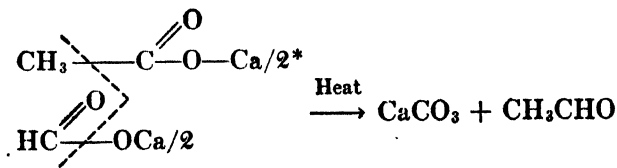
According to Wieland's theory of oxidation, this removal of hydrogen is all important, while oxygen, if present, serves only as a hydrogen acceptor. The oxidation of an aldehyde according to this theory would proceed through the following stages: (a) hydration; (b) loss of hydrogen.



It is significant that if an aqueous solution of acetaldehyde is treated with palladium black, no free oxygen being present, the acetaldehyde is oxidized to acetic acid, and palladium hydride is formed. If oxygen is admitted, we get water and palladium. Thus we have a clear insight of the action of the catalyst. There is much additional experimental verification for the Wieland theory.

Formaldehyde is prepared from methanol on the large scale by reaction (2). Some air is admitted with the alcohol; the oxidation of a portion of the hydrogen then produces heat which promotes the main reaction. Issuing formaldehyde may be used directly for synthesis, or dissolved in water and methyl alcohol to give a solution (about 40%) called Formalin. With changes in temperature this reaction may be used to make various aldehydes besides those mentioned here. For another commercial method, see page 32.

(3) Heating the calcium salt of an organic acid with calcium formate produces the corresponding aldehyde.



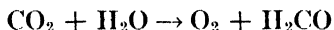
Heating calcium formate alone gives formaldehyde and calcium carbonate.

\*  $\text{Ca}/2$  stands for a half atom of calcium. This device saves doubling the entire formula.

Aldehydes are oxidation products of primary alcohols and reduction products of monocarboxylic acids. Methods (1) and (2) show preparation by oxidation of alcohols; (3) shows reduction of acids. In this preparation catalytic reduction is not practical as it cannot be halted at the aldehyde stage.

(4) The formation of acetaldehyde from acetylene is shown on page 66. This method has considerable commercial importance.

(5) There is a theory that the first step in the synthesis of sugars and other carbohydrates in plants which contain chlorophyll is the formation of formaldehyde from carbon dioxide and water:

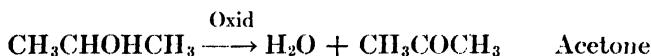


Discussion of this theory will be found in the chapter on carbohydrates.

### PREPARATION OF KETONES

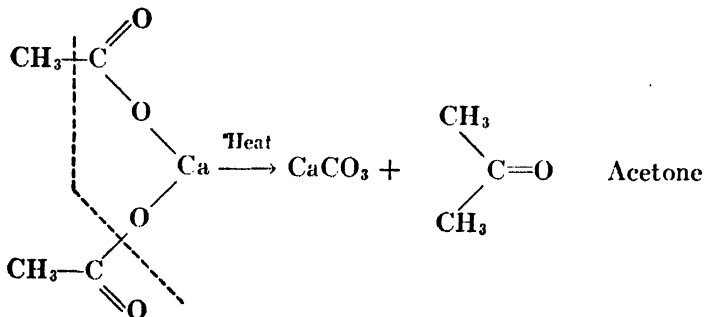
The ketones are formed by reactions analogous to (1), (2), and (3) above.

(1) By the oxidation of a *secondary alcohol* a ketone is formed:

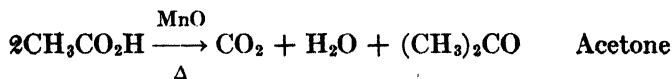


Method (2) for aldehyde preparation is conveniently used.

(2) Ketones may also be made by heating the calcium salts of the aliphatic saturated acids. Both simple and mixed ketones are made in this way by choosing the proper salts. Acetone is formed when calcium acetate is heated:



A better method involves passing the vapor of an acid or acid anhydride over a heated catalyst (metal or metal oxide). This method may be used for a number of ketones; it is illustrated below for acetone, some of which is made commercially in this way.



(3) The dry distillation of wood yields some acetone, but this method would not begin to supply the present demand. Large amounts of acetone are produced by bacterial fermentation of corn starch or molasses, butyl alcohol being produced in even greater yield at the same time (pages 99, 790). Acetone production by oxidation or dehydrogenation of isopropyl alcohol (obtained by hydration of propene) competes seriously with production by the fermentation method.

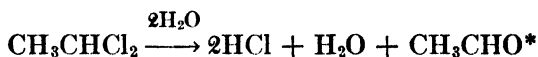
Special methods for the formation of ketones are: (4) the Grignard reaction (page 573), and (5) the use of acetoacetic ester (page 211). Small amounts of acetone normally occur in blood and urine; in cases of diabetes the amount is greatly increased.

#### MOLECULAR STRUCTURE OF ACETALDEHYDE

If we give C, H, and O their customary valencies, there is only one formula possible for formaldehyde, namely  $\text{H}_2\text{C}=\text{O}$ . This formula accords with the chemistry of the compound, since it illustrates unsaturation. For acetaldehyde we would be inclined to accept an analogous structure,  $\text{CH}_3\text{CH}=\text{O}$ , however there are two other possibilities,  $\text{CH}_2=\text{CHOH}$  and  $\text{CH}_2-\text{CH}_2$ . The latter does not answer; we have already used this formula



for ethylene oxide, which we know is formed by dehydration of ethylene glycol, a compound whose two OH groups are on adjacent carbon atoms (page 108). Acetaldehyde is formed by dehydration of a dihydroxy compound **both of whose OH groups are on the same carbon atom**. We prove this fact when we make acetaldehyde by the hydrolysis of 1,1-dichloroethane (ethylidene chloride):



The ethylene-alcohol formula finds strong support in certain reactions of acetaldehyde, and in the existence of derivatives of the general formula  $\text{CH}_2=\text{CHOR}$ . For the present, then, we will write the formula of acetaldehyde and other aldehydes with the  $-\text{CHO}$  group because most of the reactions justify this structure. Later it will be necessary to consider the other possible formula given above.

#### CHEMICAL REACTIONS OF ALDEHYDES

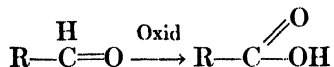
The reactions of aldehydes include oxidation, reduction, addition, substitution, polymerization, as well as some special reactions which do not come under these headings. Because of the large number of reactions in which they take part, the aldehydes are very useful synthetic agents. The following examples show those reactions which are general to the

\* The method of preparation shown in this equation and the preparation of acetaldehyde from ethyl alcohol both prove that the two carbons of the aldehyde are joined to each other.



series; special reactions of the first member, formaldehyde, will follow in a separate section.

(1) *Oxidation.* An aldehyde on oxidation forms an acid with the same number of carbon atoms.

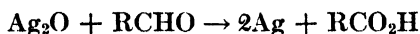


A theory regarding the mechanism of this reaction has already been discussed. Aldehydes may readily be oxidized to acids by solutions containing silver ion, precipitating the metal in the form of a mirror. The reduction of an ammoniacal solution of silver nitrate is one of the tests commonly used for detection of the aldehyde group. Aldehydes also reduce Fehling's solution\* yielding a reddish precipitate of cuprous oxide; at times a small amount of metallic copper is precipitated. The oxidizing agent in Fehling's solution is essentially cupric hydroxide; that of the ammoniacal silver nitrate is essentially silver oxide.

Equation for action of Fehling's solution:

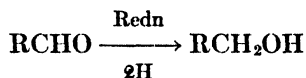


Equation for action of silver nitrate:



Commercially acetakdehyde is oxidized to acetic acid by air in the presence of manganese acetate.

(2) *Reduction.* Primary alcohols result from the reduction of aldehydes.

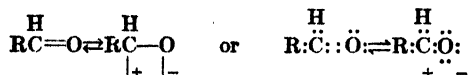


The reduction may be performed by the use of a copper catalyst and hydrogen; it represents the reversal of method (2), page 137. At low temperature hydrogenation takes place; above 200° the equilibrium shifts increasingly toward the dehydrogenation. One may also reduce an aldehyde with chemical reducing agents (metal and acid). See also page 491.

(3) *Addition reactions.* The C=O (carbonyl) group of aldehydes behaves in some respects like the C=C union in an olefin. Under the influence of certain reagents the double bond is ruptured† and addition

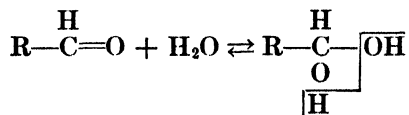
\* Fehling's solution (A) contains sodium hydroxide and Rochelle salt (sodium potassium tartrate). Solution (B) contains copper sulfate. These solutions are mixed in equal parts and diluted with water at the time the test is performed. (See also page 264.)

† It would be more accurate to say that a certain number of molecules have an "activated" open bond, ready for addition reactions. Such molecules are in equilibrium with the normal molecules.



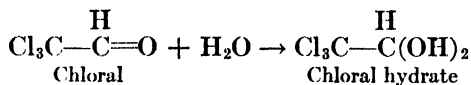
takes place with the formation of new compounds.\* In all of these cases we find that the more positive part of the reagent joins to the oxygen of the aldehyde, and the more negative part to the carbon. Some of the important addition compounds of the aldehydes are shown in the following examples.

(a) Addition of water.

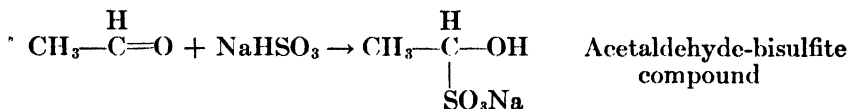


In water solution the equilibrium shown here may be assumed to exist; however the dihydroxy compound is in most cases too unstable to be isolated. A stable compound is formed when, instead of a simple aldehyde, we use a substituted aldehyde with halogen in place of hydrogen.

**Example:**



(b) Addition of sodium bisulfite.



The formation of bisulfite compounds is often a means of separating an aldehyde from other compounds with which it may be mixed. The aldehyde is easily regenerated when the bisulfite compound is treated with either dilute acids or bases.

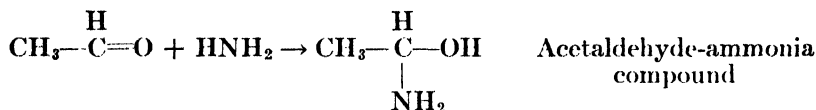
Formaldehyde sodium bisulfite gives upon reduction sodium formaldehydesulfoxylate, Rongalite,  $\text{H}_2\text{C}(\text{OH})\text{SO}_2\text{Na}\cdot\text{H}_2\text{O}$ , which is used as a reducing agent, especially in discharge dyeing.

The reaction with sodium bisulfite probably has something to do with the Schiff test for aldehydes. In this test a solution of an aniline dye is decolorized with sulfurous acid. Upon addition of an aldehyde a red or purple color appears. The reaction was explained on the basis of the

\* **Digression.** The halogens do not add to the C=O group of the aldehydes as might be expected from a consideration of the ethylene double bond, but react in an altogether different manner (page 144). One may make the general statement that unsaturation in a molecule always shows the possibility of addition reactions. However, the kind of additions that can take place is conditioned by the nature of the atoms holding the double bond and also, to some extent, by the shape and size of the rest of the molecule. For this reason we shall find some differences between the additions of aldehydes and ketones. Ketones, having two alkyl groups on the carbonyl carbon are more "crowded" than aldehydes, and there is less room for new groups to come in. If the ketone is substituted near the carbonyl group the crowding is intensified. Thus hexamethylacetone  $(CH_3)_3C(C=O)C(CH_3)_3$  does not add reagents which commonly add to ketones.

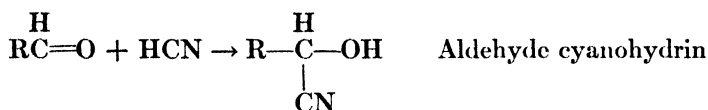
addition of the sulfurous acid to the aldehyde, but has been shown to be much more complex than that.

(c) Addition of ammonia.



The aldehyde-ammonia compound precipitates when ammonia gas is passed into a dry ethereal solution of the aldehyde. Aldehydes are easily regenerated when these solid ammonia addition-products are heated with dilute acids. The formation of these compounds is a simple way to isolate aldehydes from mixtures, at least in some cases.

(d) Addition of hydrogen cyanide:

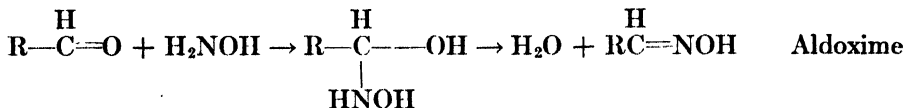


Aldehyde cyanohydrins are valuable synthetic compounds. See, for example, amino acids, hydroxy acids. A somewhat better synthesis than the one shown above is from a bisulfite compound and a cyanide:



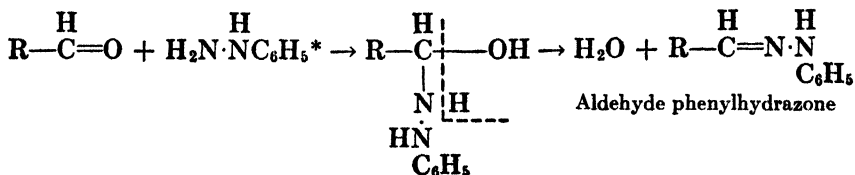
This method avoids the use of hydrocyanic acid, which is poisonous. Action of a trace of free sodium bisulfite upon the cyanide releases hydrogen cyanide which quickly adds to the aldehyde present in the mixture (in equilibrium with its bisulfite compound). This causes the breakdown of more molecules of the bisulfite compound, releasing additional sodium bisulfite, etc.

(e) Addition of hydroxylamine.



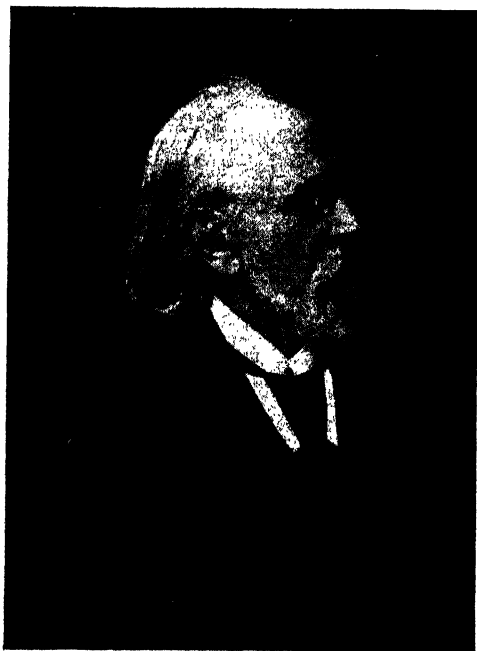
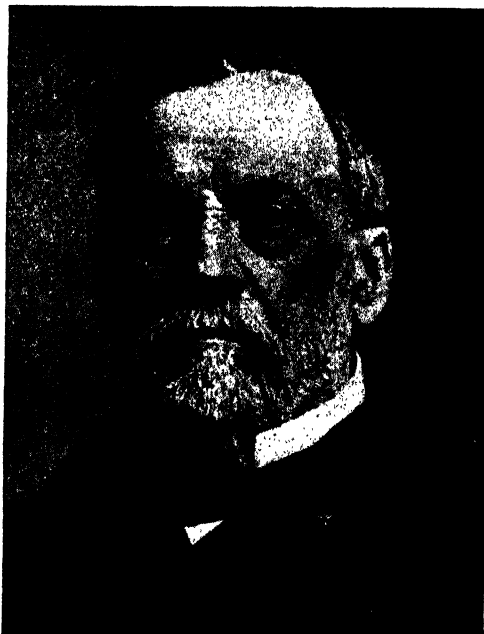
The reaction of hydroxylamine with an aldehyde results in the loss of water and formation of a compound called an oxime. Such compounds are named from the aldehyde put in reaction, as acetaldoxime (ethanal oxime), etc.

(f) Addition of phenylhydrazine. A phenylhydrazone is formed:



\* The  $\text{C}_6\text{H}_5$  group or radical, known as the phenyl radical, will be taken up for study in the chapter on benzene compounds, page 396.

**LOUIS PASTEUR.** (1822-1895, French.) Chemists are chiefly interested in his work with tartaric acid, his methods for effecting the resolution of racemic mixtures, and some of his fermentation studies. See *Am. Chem. J.*, **17**, 798 (1895), *J. Chem. Soc. (London)*, **71**, 683 (1897), *J. Chem. Education*, **5**, 50 (1928), *ibid.*, **11**, 614 (1934). Vallery-Radot, *Life of Pasteur* (Doubleday, Page Co., 1926); also this book, page 333.



**R. A. C. EMIL ERLLENMEYER.** (1825-1909, German.) Erlenmeyer was a student of Kekulé, much interested in the structural theories of organic chemistry. Students know him best through his naphthalene formula and the conical flask named after him. See *J. Chem. Soc. (London)*, **99**, 1649 (1911); also this book, page 586.

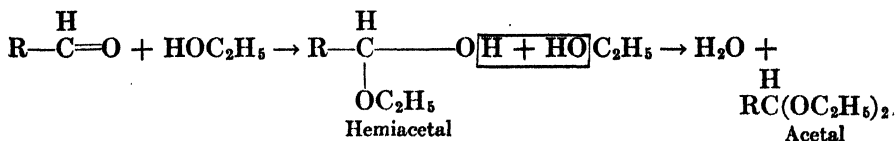
All of the reactions shown above are additions at the  $C=O$  double bond of unlike positive and negative atoms or groups. The products are more or less easily hydrolyzed, returning the original substances, aldehyde and reagent. However, in the case of the cyanohydrin, hydrolysis with strong mineral acids yields a new compound, belonging to the series of hydroxy acids (see page 238).

The oximes and phenylhydrazones of the aldehydes crystallize well in most cases, have definite melting points. For this reason they are often made in order to identify specific aldehydes (page 544). The semicarbazones, made from semicarbazide and aldehydes are also useful in this role. See page 273.

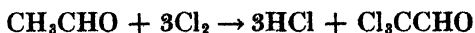
Since many of the aldehydes and ketones are liquids and the identification of a small amount of liquid is difficult, it is very convenient to convert these compounds to these solid derivatives. The student has learned by now that the purification of a small amount of solid is a practical operation and that a melting point determination can be made with very little material.

This identification of compounds is frequently necessary in the course of organic research work because most reactions give by-products, sometimes in quite good yield. After a chemist has separated and purified such a compound he first makes a sufficient number of tests to be sure of the classification of the compound. He then prepares one or more solid derivatives and checks their melting points against recorded values, and in this way learns which particular member of a homologous series he has in hand. It is of course understood that this method can be used only with well known compounds, a number of whose solid derivatives are already listed in tables. For such compounds the scheme described is very suitable, as it avoids the necessity of quantitative analysis and molecular weight determination, which are time-consuming operations. For new compounds such analysis is necessary in addition to the tests which establish the homologous series to which the compound belongs.

(g) Reaction with alcohols. In the presence of hydrochloric or sulfuric acid, aldehydes react with alcohols to form compounds called acetals. An unstable hemiacetal is an intermediate compound in the reaction. Acetals are used in synthesis. These substances, like the other aldehyde derivatives which have been shown, hydrolyze (to return the aldehyde and alcohol from which they were formed). Acids catalyze the hydrolysis; bases do not.

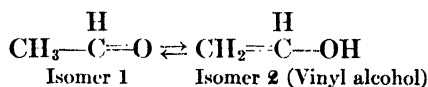


(4) *Reaction with halogens.* The hydrogen of the alkyl group next to carbonyl is replaced by halogen atom.



This replacement of hydrogen of acetaldehyde by halogen is a rapid reaction, even at room temperature. An explanation of this may be found in the dual structure possible to compounds which have alkyl group joined to carbonyl.

Such compounds, by virtue of the mobility of the alkyl hydrogen conferred by the near presence of the carbonyl group, may exist in two structural forms. These two forms for acetaldehyde are as shown below.



Isomer 1 above may be called the ordinary or stable form of an aldehyde (acetaldehyde is used as an example). Isomer 2 represents an unsaturated alcohol (in this case, vinyl alcohol). Compounds of the type of vinyl alcohol, in which OH group is attached to a doubly-bound carbon atom, have never been isolated; however, there is strong evidence that they exist, at least in small concentration, in the presence of their isomeric aldehydes. Derivatives of such compounds as vinyl alcohol are quite common.

When these derivatives are treated in such a way that vinyl alcohol should be formed, acetaldehyde is invariably the product of the reaction. Thus, the hydrolysis of ethyl vinyl ether,  $\text{CH}_2=\text{CHOC}_2\text{H}_5$ , does not yield ethyl alcohol and vinyl alcohol, but ethyl alcohol and acetaldehyde.

Acetaldehyde shows by several of its reactions that it may easily pass to the vinyl alcohol structure. Thus, when it is dissolved in dilute sodium hydroxide solution and treated with a mercury salt, a derivative of vinyl alcohol is precipitated.

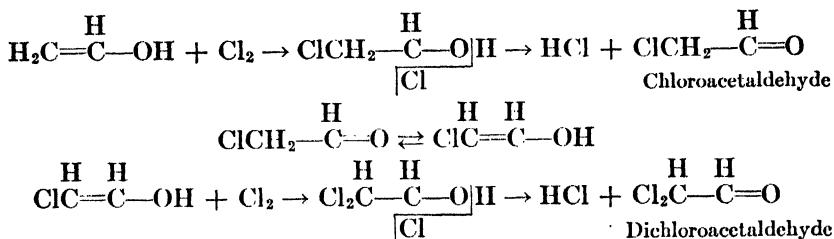
A shifting of hydrogen atom as illustrated in these examples, appears in

H

all compounds with the grouping  $\text{M}=\text{C}-\text{OH}$ .<sup>\*</sup> All such compounds may therefore exist in two forms. Spontaneous isomerism of this kind is called *tautomerism*. The particular type of tautomerism illustrated here is the *keto-enol* type, the aldehyde tautomer being keto (it has the  $\text{C}=\text{O}$  group typical of ketones), and the alcohol form enol (this name is derived from *alkene-alcohol*). In some instances, both tautomers are capable of independent existence, as is true with acetoacetic ester (page 210). Sometimes, as in the case of acetaldehyde, one form appears to be much more stable than the other. Ordinarily, they coexist in equilibrium with each other in a sample of a tautomeric substance. Any reaction which tends to remove one tautomer will disturb the equilibrium relations; as predicted by the law of mass action, the tautomer which is removed will be replaced by sacrifice of the other tautomer.

<sup>\*</sup> The letter M represents any structure which may occur with the group in question. See page 209 for further discussion of tautomerism.

It seems probable that the alcohol type of acetaldehyde takes part in the reaction with halogens as follows:

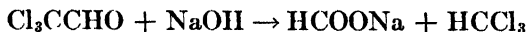


Several repetitions of the above type of reaction would lead to the production of  $\text{Cl}_3\text{CCHO}$ , trichloroacetaldehyde, or chloral. The fact that iodine will replace alkyl hydrogen of an aldehyde, while unable to do so with saturated hydrocarbons, leads one to suspect this new type of reaction in the case of the aldehydes. Likewise, the speed of the reaction of halogens with aldehydes becomes rational if aldehydes can have an ethylene structure.

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**Chloral.** Trichloroacetaldehyde or chloral,  $\text{Cl}_3\text{CC}=\text{O}$ , whose formation is shown above, is perhaps the most important of the chlorinated aldehydes. This substance is an oily liquid with an odor suggestive of acetaldehyde. As would be expected, chloral shows the reactions typical of aldehydes. It has already been shown that chloral forms a stable compound with water. The product of this reaction is a solid, chloral hydrate. It is used in medicine as a hypnotic. Technically chloral is made by prolonged action of chlorine upon alcohol; oxidation to aldehyde is probably the first step of the synthesis. The aldehyde is next chlorinated to chloral which adds alcohol to form a hemiacetal,  $\text{Cl}_3\text{CCH}(\text{OH})\text{C}_2\text{H}_5$ . Treatment of this compound with sulfuric acid gives chloral.

The hydrolysis of chloral yields chloroform and a salt of formic acid:



Oxidation of chloral gives trichloroacetic acid; reduction gives trichloroethanol,  $\text{Cl}_3\text{CCH}_2\text{OH}$ . Avertin (page 107) is made by reduction of tribromoacetaldehyde.

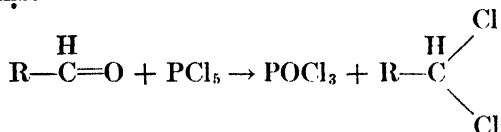
**Iodoform,  $\text{CHI}_3$ ,** is produced when ethyl alcohol or acetone is treated with iodine and alkali. We may assume that the alcohol is first oxidized to aldehyde by the iodine, after which iodine is taken up by the aldehyde, as indicated in the above equations showing the reaction with chlorine. Hydrolysis is the final step, by means of which iodoform and a salt of formic acid are set free. The number of reactions involved in the transformation may explain why the iodoform does not immediately make its appearance. As said before, the iodoform test is not specific for ethyl alcohol. Any compound having the  $\text{CH}_3\text{CO}$  group joined to C or H, or any compound

which (like alcohol in the above example) will yield this group, will give the test. The test has recently been improved by employing dioxane as a solvent.

This reaction in which an alcohol, aldehyde, or methyl ketone is treated with halogen and alkali to yield iodoform (chloroform, bromoform) is known as the **haloform reaction**. Acetaldehyde is the only aldehyde giving the test; hence ethyl alcohol is the only primary alcohol which responds. Of secondary alcohols, only those with the group  $\text{—CH(OH)CH}_3$  give the test.

#### FURTHER REACTIONS OF ALDEHYDES

(1) *Reaction with phosphorus pentachloride.* Replacement of oxygen by chlorine atoms:



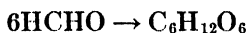
Halogen compounds of this type revert to the original aldehydes on hydrolysis.

(2) *Polymerization of aldehydes.* Aldehydes resemble the true unsaturated compounds we have taken up (ethylene, acetylene) in the ease with which their molecules come together to form the aggregates called polymers. Thus, for formaldehyde several of these substances are known.

*Paraformaldehyde*,  $(\text{HCHO})_x$ , a solid formed by evaporating an aqueous solution of formaldehyde. Heat regenerates formaldehyde from this substance; it is therefore employed for fumigation ("Paraform").

*Trioxymethylene*,  $(\text{HCHO})_3$ , a crystalline solid, formed from liquid formaldehyde.

*Formose.* When formaldehyde is allowed to react for some time in dilute solution with calcium hydroxide, polymerization takes place in the sense of the following equation:



A mixture of substances is formed called formose, which in many ways is similar to the simple sugars (page 364).

Acetaldehyde also forms more than one polymer.

*Paraldehyde.* Acetaldehyde treated with a drop of concentrated sulfuric acid polymerizes violently to paraldehyde, a liquid of boiling point  $124^\circ$ , having the formula  $(\text{CH}_3\text{CHO})_3$ . This substance shows none of the typical reactions of aldehydes, but may be converted to acetaldehyde by heating with dilute acid. Paraldehyde is employed in medicine as a soporific.

*Metaldehyde.* When treated with acid at low temperature, acetaldehyde polymerizes to metaldehyde,  $(\text{CH}_3\text{CHO})_4$ , a solid substance, which, like



paraldehyde, does not display aldehyde properties. Acetaldehyde is formed from metaldehyde when the latter is heated with sulfuric acid. The following structures have been proposed for paraldehyde and metaldehyde. The lack of aldehyde properties is illustrated by the absence of carbonyl groups in these structures.

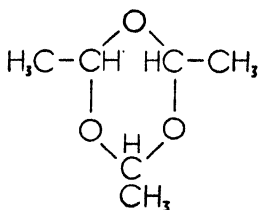


FIG. 26.

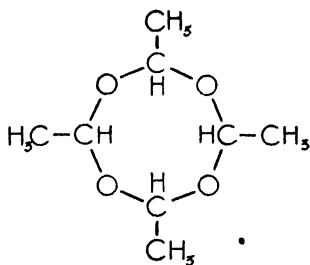
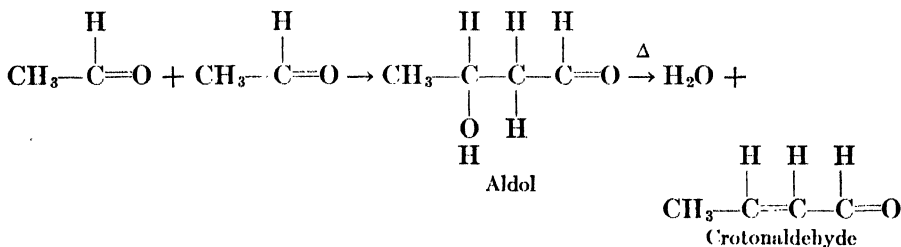
Paral-  
dehyde

FIG. 27.

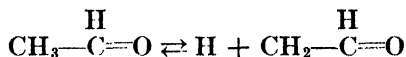
Metal-  
dehyde

The lower members of the aldehyde series (excepting formaldehyde), when treated with strong base, polymerize or condense to yellowish resin- or gum-like substances called aldehyde resins.

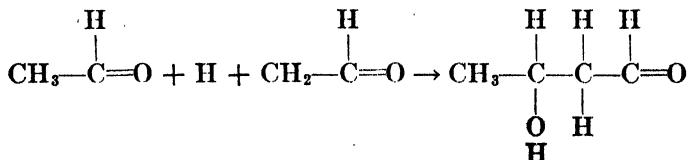
(3) *The aldol condensation.* This is a type of reaction common to aldehydes, ketones, etc., by means of which carbon atoms are brought together, resulting in production of a longer chain. The reaction, as shown below for acetaldehyde, takes place when this substance is treated with dilute alkali or zinc chloride.



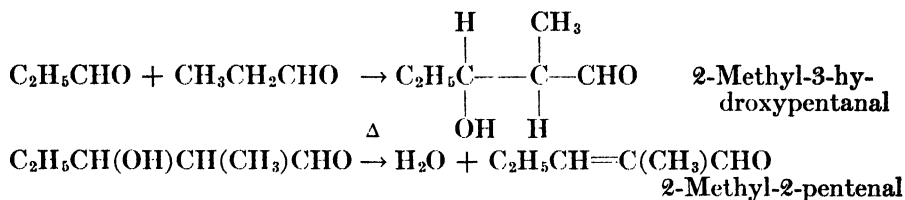
In this reaction absorption takes place *as if* a molecule of aldehyde separated as follows:



the two parts then joining to a second molecule of aldehyde in the same manner as in the addition of HCN, NH<sub>3</sub>, etc.



In reactions of this kind, the hydrogen absorbed is always on carbon next to a carbonyl (keto) group (so-called  $\alpha$  hydrogen). The mobility of alkyl hydrogen atoms when situated next to carbonyl has already been discussed under the subject of tautomerism, page 145. Propionaldehyde or any other homolog of acetaldehyde would give a branched-chain compound:



The substance 3-hydroxybutanal, obtained by condensation of acetaldehyde with itself, has the type reactions of aldehydes, and also possesses a hydroxyl group; this accounts for naming it aldol (*aldehyde alcohol*). When treated with dehydrating agents or distilled, crotonaldehyde is produced by loss of water. Reactions of the type considered here are called *condensations*. A **condensation** is a reaction involving union between atoms in the same or different molecules (possibly molecules of two different compounds) to form a new compound of greater complexity, frequently of greater molecular weight. Aldol reverts in part to acetaldehyde when distilled, and aldol condensations in general are reversible.

The aldol condensation has considerable importance in synthetic work; other examples of this reaction will occur from time to time in these pages. In a majority of these cases, a loss of water, as shown above, or alcohol or some stable compound, takes place as a second step in the process. A review of the reactions of aldehydes will show that the addition reactions with ammonia, hydrogen cyanide, etc. (page 142), take place in the same way as the first step in the aldol condensation, and that in some cases, (reaction with hydroxylamine, hydrazine, or phenylhydrazine) the loss of water occurs as with aldol, leaving as a final product a substance with a double bond. By definition these reactions are condensations.

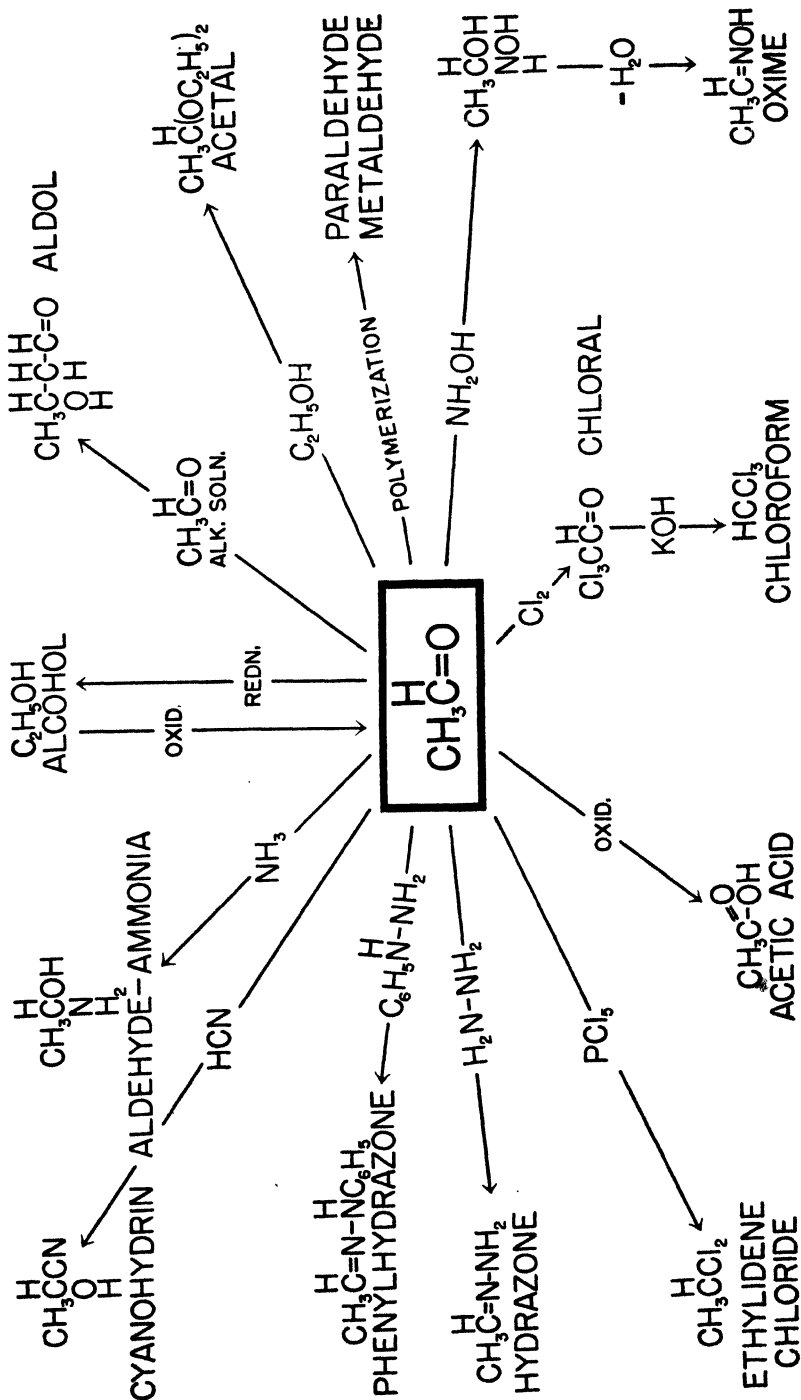
Polymerization reactions and condensations should not be confused. The chief distinguishing features of polymerization are (1) necessity of reaction between identical molecules.\* (2) In many cases the formation of a mixture consisting of molecules of many different weights. In condensation (1) we are not restricted to the use of identical molecules, (2) the reaction usually leads to definite products and but few of them. See also page 208.

(4) *Intermolecular Oxidation-reduction*. Acetaldehyde, when treated with aluminum ethoxide, oxidizes and reduces itself. One molecule forms ethyl alcohol while another is oxidized to acetic acid. The product of this

\* For definition of copolymerization, see page 504.

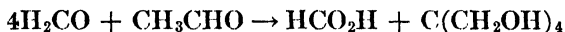


## REACTIONS OF ACETALDEHYDE



### CHART V.

(4) *Reaction with acetaldehyde.* In the presence of calcium hydroxide solution three molecules of formaldehyde react with *alpha* hydrogens of acetaldehyde. A fourth molecule acts as a reducing agent, being itself oxidized to formic acid. The product is pentaerythritol.



Nitration of pentaerythritol gives the "tetranitrate,"  $\text{C}(\text{CH}_2\text{ONO}_2)_4$ , a powerful military explosive.

(5) *Reaction to form resins.* Formaldehyde forms resins with numerous organic compounds. Such resins form when molecules produced in a reaction are too large to give ordered crystalline formation. If an organic molecule has at least two reactive groups (example, the reactive H and carbonyl of formaldehyde) it can unite an indefinite number of times with itself or with molecules of another suitable compound, unless interfering influences are present. As many molecules have the necessary bifunctional set-up, it is seen that resin formation is not at all unusual in the organic field.

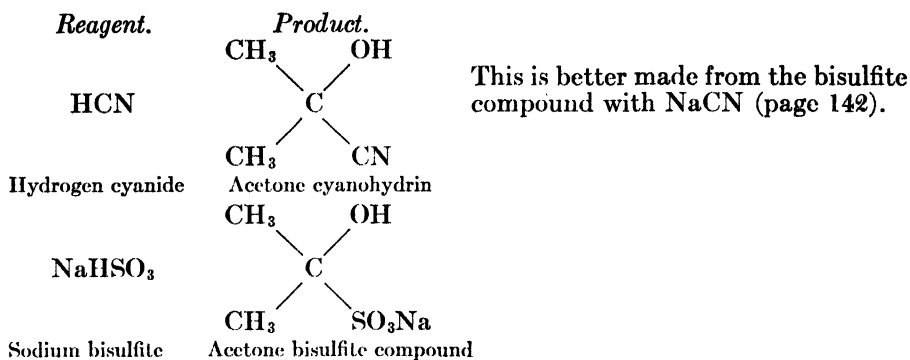
Formaldehyde gives useful resins with urea (Beetle), with casein (Galalith), and with phenol (Bakelite) (page 503). Resins will receive later attention.

**Tests for Formaldehyde.** Formaldehyde has often been used as a food preservative for which purpose it is considered to be harmful; therefore it has been necessary to have delicate tests to show its presence. In milk the presence of formaldehyde is shown by the addition of concentrated hydrochloric acid and a trace of ferric chloride. A purple color results. When a solution containing formaldehyde is mixed with a little resorcinol solution and carefully layered over concentrated sulfuric acid, a red or purple ring appears at the junction of the liquids.

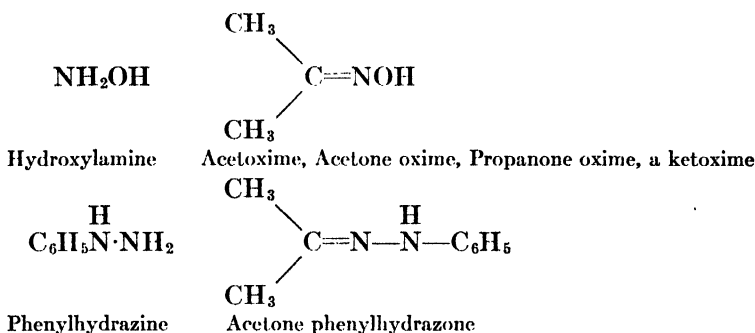
## REACTIONS OF KETONES

As we have already mentioned (page 134) the ketones and aldehydes have a similar structure; both possess carbonyl group, but whereas in the aldehydes hydrogen atom is attached to carbonyl, in the ketones two alkyl groups are linked to carbonyl. Thus many of the reactions of these two classes are identical; however the aldehydes are, in general, more reactive than the ketones. The reactions of ketones are presented in the following examples.

(1) *Addition reactions of ketones.* These reactions are in most cases similar to those of the aldehydes. They will be reviewed to show the likeness in structure of the compounds produced to those which the aldehydes form with the same reagents. Only the reagent and the final product are shown in the list below, in which acetone is used as a typical ketone.



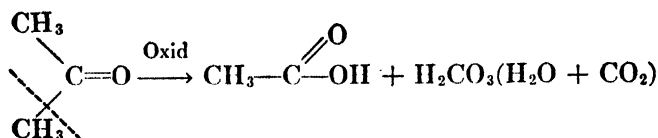
This reaction is shown only by those ketones in which one R group is methyl.



The cyanohydrin is useful for synthetic work since its hydrolysis gives a hydroxy acid. The bisulfite compound is but slightly soluble in the presence of sodium bisulfite; it is made to separate acetone from a mixture with other compounds. Treatment with base regenerates acetone. The oxime is a solid and may be used to identify acetone. The derivative with semicarbazide (a semicarbazone) is also useful for identification.

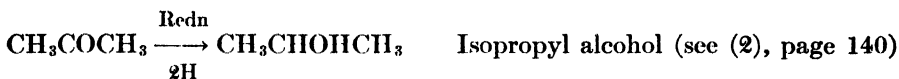
(2) *Oxidation.* A mixture of acids is produced when a ketone is oxidized.

Example:

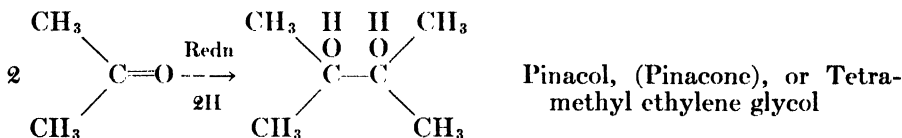


Since oxidation of a ketone involves rupture of a bond between carbon atoms, it will be understood that they are oxidized with greater difficulty than are the aldehydes. Thus ketones are unaffected by Fehling's solution or ammoniacal silver nitrate solution.

(3) *Reduction.* A secondary alcohol is the product of reduction of a ketone.

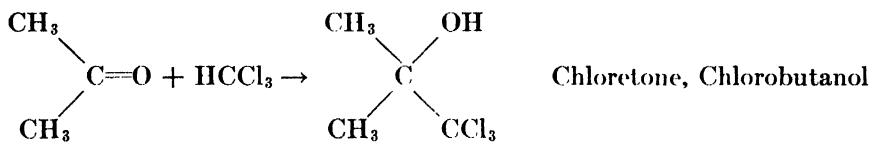


Ditertiary glycols (pinacols) may also be formed during reduction by magnesium in alkaline solution. An aluminum alkoxide may be used in



the reduction of an aldehyde or a ketone. The reaction is catalytic and is confined to reduction of the carbonyl group. This is advantageous; other reducing combinations may and do affect other functions besides the carbonyl group. For details of the method see reference 10, page 161.

(4) *Reaction of acetone with chloroform.* Formation of chloretone:



This reaction will be noted as similar to the reaction with HCN, NH<sub>3</sub>, etc. The product has value in medicine as a hypnotic, a local anesthetic.

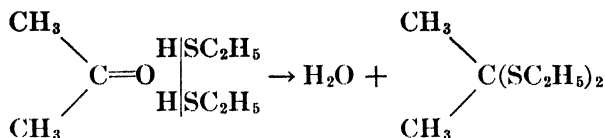
**Differences between Aldehyde and Ketone Reactions.** Oxidation is more difficult with ketones.\* Hence, solutions containing silver or copper ions, which are promptly reduced by the lower aldehydes are not affected by ketones. The oxidation of an aldehyde yields a single acid; that of a ketone a mixture of acids. Ketones do not readily form substances analogous to the acetals. (However, in this connection, see the next paragraph.) Ketones do not polymerize. Ammonia reacts with them to form complex condensation products. The Schiff reaction generally fails, though acetone does give the test after some time.

### FURTHER REACTIONS OF KETONES

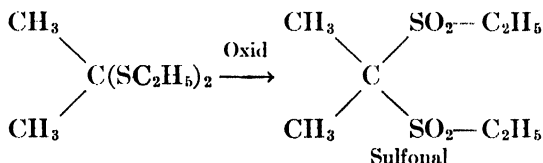
(1) The thioalcohols form compounds with ketones similar in structure to the acetals, although oxygen alcohols do not react in this manner with them.† Thus acetone reacts with ethanethiol as follows:

\* That is, with unsubstituted ketones; those which have a hydroxyl group on the carbon next to carbonyl are oxidized by Fehling solution or ammoniacal silver nitrate solution (see page 351).

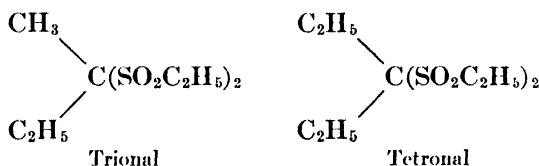
† The ketone-acetals may however be made by indirect synthesis. They are easily hydrolyzed by dilute acids.



The product obtained from this reaction yields sulfonal when it is oxidized.

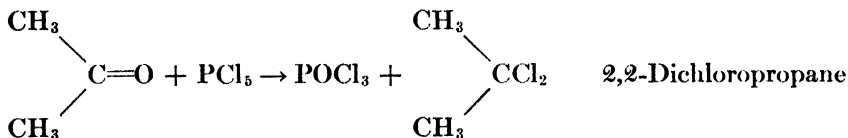


Trional and Tetronal are formed by a similar series of reactions.

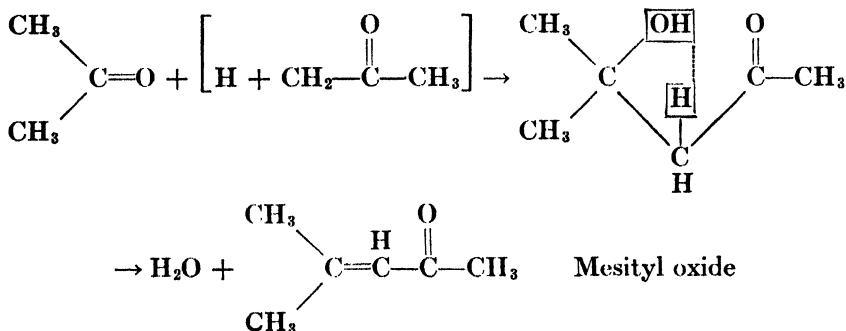


Sulfonal and trional have been employed in the field of medicine as hypnotics and sedatives. Tetronal has greater hypnotic power than sulfonal, but is very slow in its action.

(2) *Reaction with phosphorus pentachloride.* This reaction is in all respects similar to that of aldehydes with this reagent.

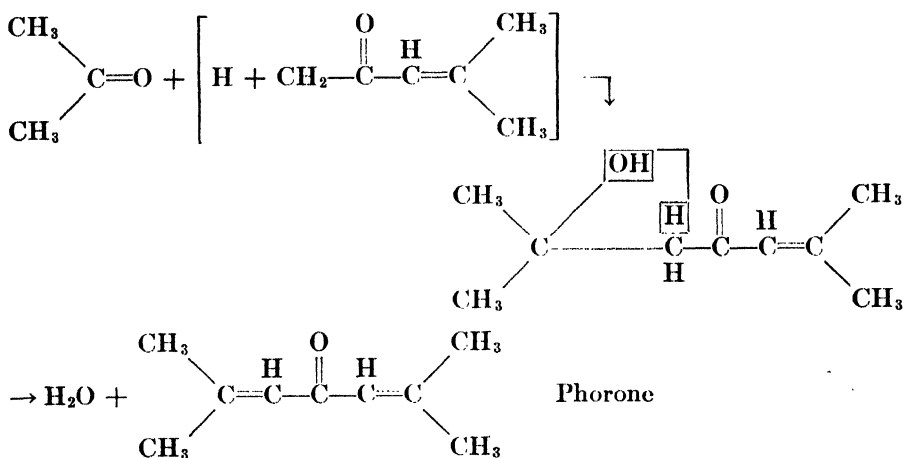


(3) *Aldol condensation.* Acetone, treated with HCl, condenses with itself to form mesityl oxide:

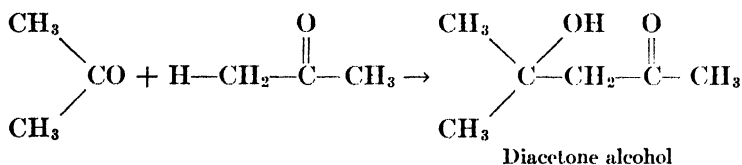




By a repetition of this reaction, phorone is formed:

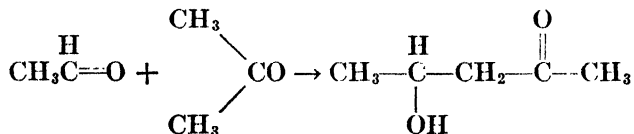


When acetone is condensed in presence of barium hydroxide we obtain diacetone alcohol:



This is recommended as a solvent because it is both an alcohol and a ketone. When it loses water it yields mesityl oxide.

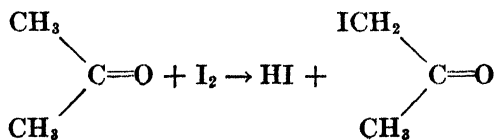
Acetone or another ketone may undergo aldol condensation with an aldehyde. Such a reaction is shown below, using acetaldehyde as an example:



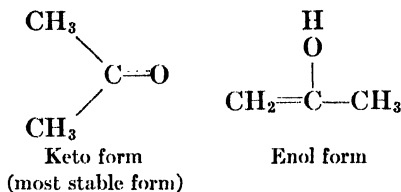
Some aldol is also produced but the acetone does not "accept" the aldehyde in an aldol condensation. This again shows that the carbonyl group is more active in the aldehyde than in the ketone.

(4) *The Haloform Reaction.* The formation of iodoform from acetone will illustrate this reaction. The probable steps are as follows:

(a) Alkyl hydrogen is replaced by iodine:



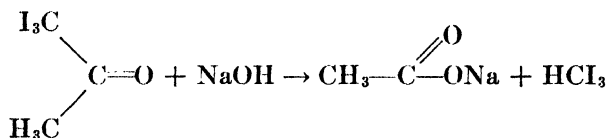
See p. 144 for probable explanation of this replacement. The tautomeric forms of acetone which correspond to those shown for acetaldehyde are:



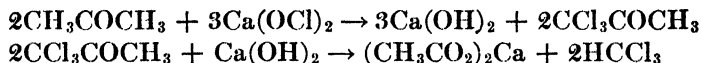
As in the case of acetaldehyde we know the enol form only through its derivatives. In the equilibrium mixture of keto and enol forms which undoubtedly exists in a sample of acetone, very little enol is present. The shift from one form to the other must be rapid. Thus, when we hydrolyze 2-bromopropene,  $\text{CH}_2=\text{CBrCH}_3$ , we get not  $\text{CH}_2=\text{C}(\text{OH})\text{CH}_3$ , but acetone.

(b) Further treatment with iodine leads to the production of triiodoacetone:  $\text{I}_3\text{C}(\text{CO})\text{CH}_3$ .

(c) Hydrolysis of the iodo compound with alkali gives iodoform and a salt of acetic acid:



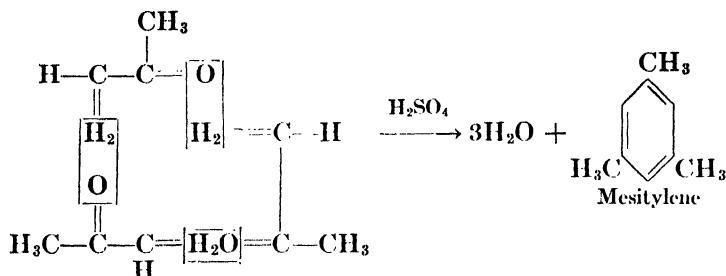
In the laboratory chloroform is often made by the action of bleaching powder upon acetone. The reaction is complex; it is sometimes explained by assuming that the bleaching powder is a source of chlorine and of calcium hydroxide, which act in a manner analogous to that shown above for the synthesis of iodoform:



The preparation of chloroform from alcohol and bleaching powder is explained similarly.

Chloroacetone,  $\text{ClCH}_2\text{COCH}_3$ , bromoacetone, and iodoacetone are easily made from the corresponding halogen with an excess of acetone. All are lacrymatory; the first two were used in World War I. Bromoacetone soon displaced chloroacetone as it is a more powerful lacrimator.

(5) *Reaction with sulfuric acid.* When a mixture of acetone and concentrated sulfuric acid is distilled, trimethylbenzene (mesitylene) passes over. This compound is formed by the condensation of three molecules of acetone, with loss of three molecules of water.



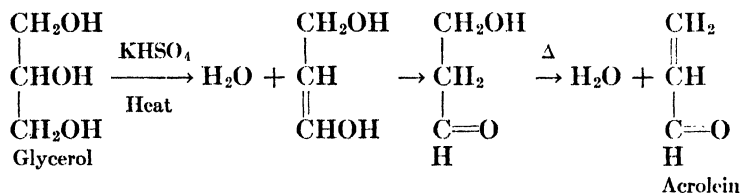
Mesitylene belongs to the ring or aromatic compounds, this reaction forming one method of passing from aliphatic to aromatic series. (See page 406.)

### UNSATURATED ALDEHYDES AND KETONES

These substances contain the structures of unsaturated hydrocarbons together with aldehyde or ketone grouping. As would be expected, they combine the reactions common to the two groups in the compound.

Examples:

Acrolein or acrylic aldehyde. The formation of this aldehyde by the dehydration of glycerol is shown in the following equation:



When fats are overheated some acrolein is produced from the glycerol which is released by hydrolysis of the fats.

Acrolein has a piercing disagreeable odor. Such a substance may be used as a "warning agent" in a refrigerator or a commercial gas line to call attention to a leak if even a small amount of gas escapes. Acrolein was used as a tear gas in World War I but was not a success. Crotonic aldehyde, whose structure and preparation are set forth on page 148, is an example of an unsaturated aldehyde; further examples will be found in the chapter on terpenes. Crotonaldehyde is effective as a warning agent in gas in a concentration of one pound to 1,000,000 cu. ft. Examples of unsaturated ketones have been presented in mesityl oxide and phorone.

### USES OF ALDEHYDES AND KETONES

Formaldehyde is dispensed in the form of a 35–40% solution, known as formalin, also in the form of its solid polymers. It is used as a germicide and disinfectant and to preserve foods. It has also the power of hardening and preserving albuminous tissues and is used as an embalming agent and in

leather tanning. Due to the extreme reactivity of formaldehyde towards many different substances it finds application in the entire field of synthetic chemistry, especially in the preparation of dyes and plastics (about 75% of the formaldehyde produced in 1941 was used for plastic manufacture).

The use of acetaldehyde in the form of paraldehyde has already been mentioned. Paraldehyde is useful for making vulcanization accelerators and other synthetic compounds. Many synthetic uses of acetaldehyde have been indicated in this chapter. Aldol and crotonaldehyde are both important compounds for synthesis. In addition crotonaldehyde has important applications as a solvent. Higher aldehydes are used in perfumes.

Quite a number of ketones, both symmetrical and unsymmetrical, have been made and studied. Those most used at present are acetone and ethyl methyl ketone. Acetone is principally useful as a solvent (gums, resins, lacquer components) and for synthesis of iodoform, sulfonal, and other compounds. We note its use in large amounts in the preparation of safety glass, cellulose acetate plastics, dyestuffs, explosives. U. S. sales for 1939 topped 100,000,000 pounds.

Isobutyl methyl ketone (Hexone) is a valuable solvent for nitrocellulose and gums, and in preparing lacquers with the vinylite resins. Other ketones find similar uses. Those marketed include diisobutyl ketone, amyl methyl ketone, phorone, mesityl oxide, acetonylacetone,  $[(\text{CH}_3\text{CCH}_2)_2]$ .



**Detection and Identification of Aldehydes and Ketones.** Aldehydes and ketones are neutral substances, therefore no more soluble in acid or base than in pure water. Only the first few members of the series are completely water-soluble; water-insoluble aldehydes and ketones dissolve in cold, concentrated sulfuric acid. Tests useful for the detection of the chief function of these compounds have been given in the discussion and are summarized on page 774 where identification is further discussed.

### REVIEW QUESTIONS

1. Write graphic formulas for: (a) Butyraldehyde; (b) Ethyl isopropyl ketone; (c) Butyl methyl ketone; (d) 2-Methylbutanal; (e) 3-Methyl-heptanone-4.
2. What substance when oxidized would yield the following: (a) Propionaldehyde? (b) Ethyl methyl ketone? (c) Butanal? (d) 3-Pentanone?
3. Show structures of compounds formed by the reaction of propionaldehyde with: (a) HCN; (b)  $\text{NH}_3$ ; (c)  $\text{NaHSO}_3$ ; (d)  $\text{NH}_2\text{OH}$ ; (e)  $\text{C}_6\text{H}_5\text{NH}\cdot\text{NH}_2$ ; (f)  $\text{C}_2\text{H}_5\text{OH}$ .
4. Write structural formulas of the derivatives formed from 2-butanone and the reagents listed above.
5. Outline the steps by which bromoform is produced from ethyl alcohol, bromine, and KOH solution.
6. Write formulas for the compounds which would be formed by the rearrangement of the following: (a)  $\text{CH}_3\text{—CH=CHOH}$ ; (b)  $(\text{CH}_3)_2\text{C=CHOH}$ .
7. What substances could be formed by the condensation of acetaldehyde with acetone?
8. Write formulas for the products of oxidation of: (a) Butyraldehyde; (b) Methyl propyl ketone.

9. Show the steps by which iodoform may be made from iodine, methyl ethyl ketone, and KOH solution.
10. How could the following mixtures be separated: (a) Ether and acetone? (b) Acetone and methyl alcohol?
11. A certain substance is either an alcohol, an aldehyde, or a ketone. What tests could be used to determine its identity?
12. Give structures of substances having the formula  $C_3H_6O$ , and state clearly how they may be distinguished from each other by use of definite tests.
13. Explain how acetaldehyde could be used as a source of compounds having a four-carbon chain.
14. Why not write the formula for an aldehyde  $RCOH$  instead of  $RCHO$ ?
15. Will aldol reduce Fehling's solution? Why?
16. Give clear definitions for the following terms: condensation; bisulfite compound; polymerization; Fehling's test; Schiff's test.
17. When  $O_2$  and ethylene are heated to a high temperature, some formaldehyde is produced. Can you explain?
18. Would you expect metallic sodium to react with an aldehyde or a ketone? Why?
19. What are the "functions" of acetaldehyde? List reactions specific for each function named.
20. Make a chart showing the relationships of acetaldehyde to: (a) Ethylidene chloride; (b) Acetylene; (c) Ethyl alcohol; (d) Acetic acid.
- (R)21. When acetaldehyde is treated with acetic anhydride, ethylidene diacetate,  $CH_3CH(OCOCH_3)_2$ , is formed. What does this show with reference to the structure of acetaldehyde?
22. Discuss the action of bases upon aldehydes.
23. Why should condensation reactions or additions be difficult in the case of a ketone with large and highly branched groups attached to the carbonyl radical?
24. Why should diacetone alcohol be a good solvent? Should it be more or less water-soluble than mesityl oxide? (Check your answer by reference to a handbook.)
25. Which is a more "definite" reaction, condensation or polymerization? Explain your answer.
26. What tests decisively show that a given compound is an aldehyde, not an alcohol?
27. A compound is suspected of being an aldehyde. Outline the tests which should be applied to it and the outcome of each test, if the compound is indeed an aldehyde.
28. Write a graphic formula for trioxymethylene.
29. Write a balanced equation for the oxidation of ethyl alcohol to acetaldehyde, using as oxidizing agent potassium dichromate (with water and sulfuric acid). The end-products are aldehyde, water, and the sulfates of potassium and chromium.
30. Write equations for reactions of formaldehyde which are not common to higher aldehydes.
31. Can trimethylacetaldehyde undergo aldol condensation with itself? Why? Can it "accept" acetone in an aldol condensation? Why?
32. Indicate how a mixture of acetone, methanol, and acetic acid may be separated. In what commercial process is such a mixture secured?
33. Four liquids are said to be ethyl iodide, acetone, *n*-butyraldehyde, and hexane. Outline a small number of decisive tests to establish the identity of each liquid.
34. What solid compounds are used to identify aldehydes and ketones? Write equations showing reactions used to form these derivatives from diethyl ketone.
35. What is tautomerism? How is it known that acetaldehyde is a tautomeric compound?
36. Write a list of specific medical applications of two aldehydes and one ketone mentioned in this chapter.
37. Discuss those points in which chloral differs from a typical aldehyde.
38. Illustrate the following transformations by the use of equations.

- (a)  $C_2H_5OH$  to  $HCl_3$ ;  
 (b)  $CH_3CO_2H$  to  $(CH_3)_2CO$ ;  
 (c)  $C_2H_5OH$  to  $CH_3CH(OC_2H_5)_2$ ;  
 (d)  $C_2H_5OH$  to  $CH_3CHCl_2$ .
39. Write graphic formulas of three compounds with the molecular formula  $C_4H_8O$ . Will any one of these compounds give the iodoform test?
- 40.\* The compound (A) contains 69.77% C and 11.63% H. Its vapor density ( $H_2 = 1$ ) is 43. (A) does not reduce Fehling solution. It does, however, form a bisulfite compound, and it gives a positive iodoform test. What is its structure?
- (R)41. Analysis of the compound (A) gives the following results: combustion of a 0.050 g. sample yields 0.1257 g.  $CO_2$  and 0.03857 g.  $H_2O$ . When (A) is treated with bromine-water the compound (B) containing 69.57% Br is formed. Reaction with HI gives (C) which contains 64.13% iodine. Treatment of (A) with a mild oxidizing agent yields the monocarboxylic acid (D). A 0.20 g. sample of (D) requires 24.22 cc. of 0.096N NaOH solution for its neutralization. Write equations for the reactions discussed here. Give a set of equations showing the synthesis of (D) from ethylene.
42. The compound (A) is a colorless liquid of unpleasant odor, soluble in water, alcohol, and ether. It reacts with sodium, but does not reduce Fehling solution. Mild oxidation of (A) with dilute permanganate solution yields the compound (B) which contains 64.30% C and 7.14% H. (B) will reduce ammoniacal silver nitrate solution. Reaction of (B) with bromine-water yields the compound (C) which contains 74.1% Br. Indicate by a series of equations how the compound (B) may be made from 1,2,3-trichloropropane.

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\* See footnote, page 119.

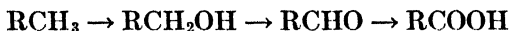
## CHAPTER VIII

### MONOCARBOXYLIC ACIDS, THIOACIDS, SALTS

Monocarboxylic acids form a large and interesting group of compounds, whose representatives and derivatives are widely distributed in nature. Several of the lower members are found free in nature; those with more than four carbon atoms are present as glycerol esters in the natural fats and oils. Traces of palmitic, oleic, linoleic, and linolenic acids have been found in starches. Naturally occurring acids from  $C_{10}$  on have normal chains and, with but few exceptions, they have an even number of carbon atoms. The acids are extremely adaptable compounds, forming a number of important derivatives, the properties of which make them useful in chemical synthesis and in the arts.

Organic acids, like other acids already familiar to us, taste sour in water solution, redden blue litmus paper, and neutralize bases to form salts. Aldehydes, ketones, and certain alcohols, although they do show very faint acidic properties in that they permit replacement of a hydrogen atom by an active metal, are not classed as acids because their acidic powers are too feeble, and are shown only with special conditions.

We have noted (pages 102, 140) that acids are obtained by the oxidation of alcohols or aldehydes.



These are the monocarboxylic acids;\* in them the oxidized carbon atom has reached its third stage of oxidation. Further oxidation would produce carbon dioxide.

The  $\begin{array}{c} \text{O} \\ \parallel \\ \text{C}-\text{OH} \end{array}$  group is called carboxyl, a name made up from *carbonyl* ( $\text{C}=\text{O}$ ) and *hydroxyl* ( $\text{OH}$ ). Due to their possession of this group, the acids here considered are often termed carboxylic acids. The saturated members of the group are called *fatty acids*, since many members of the series may be obtained by the hydrolytic decomposition of natural fats; moreover, the higher members are somewhat similar in physical properties to the fats. Saturated monocarboxylic acids form a homologous series with the formula  $C_nH_{2n}O_2$ .

The structural formula for a monocarboxylic acid is usually printed as  $\text{RCOOH}$  or  $\text{RCO}_2\text{H}$ , in order to use but one line of space. Carboxylic

\* There are other types of acids; see, for example, pages 322, 437.

acids are known with two or more carboxyl groups per molecule. Consideration of these substances will be deferred to a later chapter.

#### PHYSICAL PROPERTIES OF THE SATURATED MONOCARBOXYLIC ACIDS

The lower members of the series of acids (up to  $C_{10}H_{20}O_2$ ) are liquids. The first three members have a sharp and irritating odor and sour taste, while the remainder of the liquid acids have a foul unpleasant smell. The boiling points in this series begin at  $100^\circ C$ ; this is higher than observed for any of the series of previous chapters. The first three acids are completely water-soluble; number four is slightly soluble, and from this point the solubility lessens, and from the  $C_{12}$  acid on it is negligible. Lower acids (to  $C_{10}$ ) are volatile in steam, but those with more than ten carbon atoms cannot be distilled with steam. The solid acids are wax-like and have a soapy or greasy "feel." They are practically odorless. In the table below the formulas, boiling points, and other constants of a number of these acids are listed. For additional data see page 215.

TABLE 14.—CONSTANTS OF NORMAL MONOCARBOXYLIC SATURATED ACIDS

Common name	Official name	Formula	M.p., $^\circ C$ .	B.p., $^\circ C$ .	Sp. g., $20^\circ/4^\circ$	Ht. of comb.
Formic.....	Methanoic	$HCO_2H$	8.6	100.8	1.220	62.8
Acetic.....	Ethanoic	$CH_3CO_2H$	16.7	118.1	1.049	209.4
Propionic.....	Propanoic	$C_2H_5CO_2H$	-22.0	141.1	0.992	367.2
Butyric.....	Butanoic	$C_3H_7CO_2H$	-4.7	163.5	0.959	524.3
Valeric.....	Pentanoic	$C_4H_9CO_2H$	-34.5	187.0	0.942	681.6
Caproic.....	Hexanoic	$C_5H_{11}CO_2H$	-1.5	202.0	0.922	831
Enanthic.....	Heptanoic	$C_6H_{13}CO_2H$	-10.0	223.5	0.918	986.1
Caprylic.....	Octanoic	$C_7H_{15}CO_2H$	+16.0	237.5	0.910	
Pelargonic.....	Nonanoic	$C_8H_{17}CO_2H$	12.5	254	0.907	1287
Capric.....	Decanoic	$C_9H_{19}CO_2H$	31.5	268.4	0.889	1458
Undecylic.....	Endecanoic	$C_{10}H_{21}CO_2H$	29-30	228 <sup>160</sup>	.....	1616
Lauric.....	Dodecanoic	$C_{11}H_{23}CO_2H$	48.0	225 <sup>100</sup>	0.883	1772
Myristic.....	Tetradecanoic	$C_{13}H_{27}CO_2H$	58.0	250.5 <sup>100</sup>	0.853 <sup>70</sup>	2086
Palmitic.....	Hexadecanoic	$C_{15}H_{31}CO_2H$	64.0	269 <sup>100</sup>	0.849 <sup>70</sup>	2398
Stearic.....	Octadecanoic	$C_{17}H_{35}CO_2H$	69.3	287 <sup>100</sup>	0.847	2711

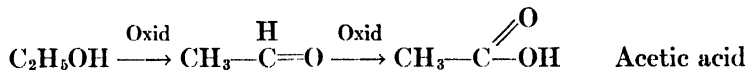
Inspection of the table above will show that the melting points of the acids if plotted against the number of carbon atoms would give a zig-zag line. Actually the melting points lie on two curves, that of the odd-numbered members lying below the other. The higher melting points of the even members is attributed to the greater symmetry of their molecules, which in turn implies stronger attraction between them.

#### METHODS OF PREPARATION

Saturated monocarboxylic acids are prepared by the following methods.

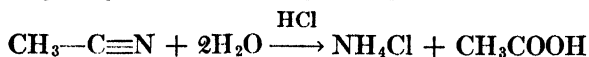


(1) By the oxidation of the corresponding\* alcohol (primary) or aldehyde:



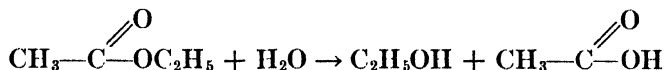
In laboratory work a dichromate in sulfuric acid solution may be used for the oxidation. The saturated acids are quite resistant to oxidation; therefore the reaction indicated here may be carried to completion without fear of destroying the acid. When an aldehyde is being formed by oxidation of an alcohol the situation is quite different (page 136). Higher acids of this series may be made by oxidation of paraffins by oxygen (air); partial oxidation gives mixtures of alcohols of high molecular weight.

(2) By the hydrolysis of the corresponding nitrile:



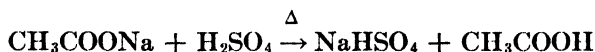
Because of this reaction, the cyanides are called the nitriles of the acids they yield on hydrolysis; thus,  $\text{CH}_3-\text{CN}$ , methyl cyanide, is called acetonitrile. The student will note that this synthesis completes the series beginning with a primary alcohol and ending with an acid having one more carbon atom, i.e.,  $\text{ROH} \rightarrow \text{RI} \rightarrow \text{RCN}$ , etc.

(3) By hydrolysis of an ester of the desired acid (page 206):



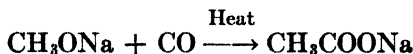
As many of the esters are found in nature, we are able by their hydrolysis to secure acids and alcohols at one step (page 97). A very important example of this reaction is found in the hydrolysis of fats (Chapter X).

(4) By the general method used in inorganic chemistry, "Distil a mixture of the sodium salt of the desired acid with a stronger, less volatile acid."† Thus, for acetic acid, we use sodium acetate and sulfuric acid:



In preparation of higher acids with high boiling points it is more practical to extract them from the water solution (with ether) than to distil them.

(5) Another method of preparation involves the reaction between an alkoxide and carbon monoxide gas:



\* By the term "corresponding" is meant a compound with the same skeleton structure of carbon atoms as the substance under consideration.

† It is obvious that there should be no possibility of a chemical reaction between the acidic reagent and the organic acid being produced.

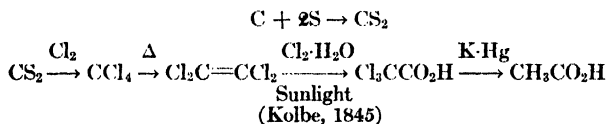
Carbon monoxide reacts with alcohols when at a temperature of about  $320^{\circ}$  and a pressure of about 150 atmospheres. A catalyst of phosphoric acid and copper phosphate is used. The method has been applied to a number of the lower alcohols giving acids (plus one carbon atom) in good yield.\*

(6) By means of the Grignard reaction which is taken up in detail on page 569 and following pages, we are able to make the carboxylic acids.

(7) By employment of acetoacetic ester or malonic ester, certain special acids may be made. The reactions will be better understood after a study of these esters has been undertaken (see page 210).

**Acetic acid is obtained commercially** in three ways: by the dry distillation of wood, a process which also yields methyl alcohol, acetone, and other substances; from the bacterial fermentation of ethyl alcohol or cider or wine; from acetylene through the intermediate formation of acetaldehyde (page 66). This is oxidized catalytically by air in the presence of manganese acetate.

It is interesting to note that acetic acid is the first organic compound which was completely synthesized in the chemical laboratory from the elements. The steps are as follows:

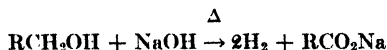


### CHEMICAL REACTIONS

The set of equations given in the next section illustrates the following **reactions of saturated monocarboxylic acids**: replacement of carboxylic hydrogen or hydroxyl group, replacement of hydrogen on the carbon next the carboxyl group. The loss of carbon dioxide from the carboxyl group by pyrolysis has already been illustrated (page 28). Another method is given on page 167.

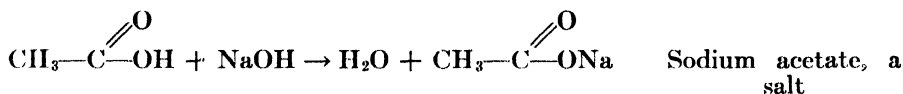
The reactions of the monocarboxylic saturated acids are of two kinds: (1) those affecting the acid group (carboxyl group), which yield substances called "acid derivatives" and (2) those affecting the alkyl group of the acid, giving the "substituted acids." Important representatives of the acid derivatives are the following:

\* Heating an alcohol to about  $320^{\circ}$  with NaOH solution gives the salt of the corresponding acid:

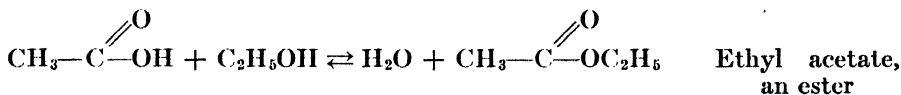


This method has been used successfully with several short-chain alcohols.

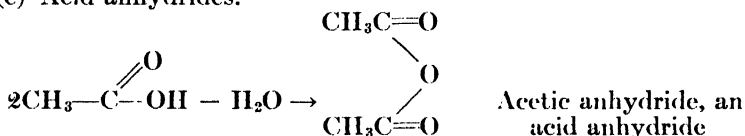
## (a) Salts.



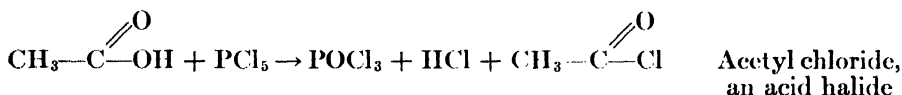
## (b) Esters.



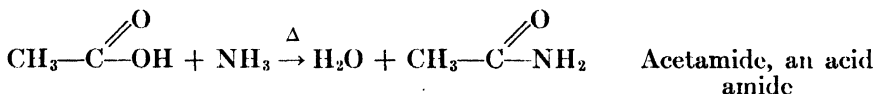
## (c) Acid anhydrides.



## (d) Acid halides.



## (e) Acid amides.

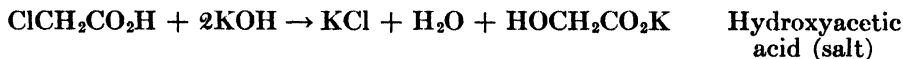


Among the substituted acids, we are particularly interested in those which follow:

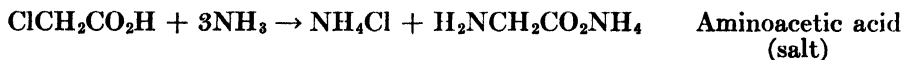
## (a) Halogen substituted acid.



## (b) Hydroxy acid.



## (c) Amino acid.

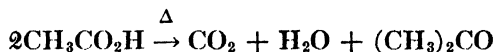


The modifications of the fatty acids which have just been passed in brief review show the great adaptability of the acids, while introducing new and interesting compounds, each of which in turn is capable of many applications. These substances, esters, anhydrides, etc., will be separately discussed in ensuing chapters; the salts alone will receive attention in the present chapter.

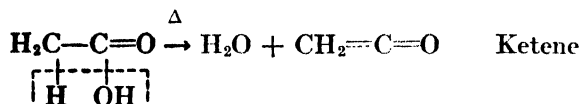
**Additional Reactions of Acids.**

(1) Formation of ketones. Acids heated in contact with certain catalysts lose the elements of carbonic acid and form ketones. As an

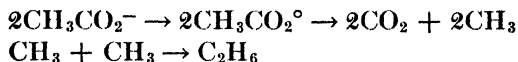
example we have the formation of acetone from acetic acid passed over hot manganese oxide or thorium oxide:



(2) Heating acetic acid alone to  $500^\circ$  causes an internal loss of water. The highly unsaturated compound ketene is formed in this way (see page 290).



(3) The electrolysis of a concentrated solution of potassium or sodium acetate gives a good yield of ethane (Kolbe synthesis, 1849). The acetate ion when discharged at the anode becomes unstable, losing carbon dioxide and liberating a free methyl group. Two such groups unite to form ethane.



This reaction, while not universally applicable, can be used with many acids to form saturated hydrocarbons as shown here.

**Discussion of Reactions. Heats of Combustion.** A survey of the reactions given for the acids shows that when an acid derivative is made from an acid, water is almost invariably a by-product (all cases cited but the formation of acid halides). Other reactions show a loss of carbon dioxide (production of methane, ethane, acetone, aldehyde), or of carbonic acid (production of ethane, of acetone).

The loss of carbon dioxide is typical of the carboxyl group; we shall note many instances of this reaction in later chapters. Due to the fact that the electrons in this group are already practically in the positions they occupy in carbon dioxide, the carboxyl group furnishes no heat on combustion. We calculate the heat of combustion of a simple acid like acetic by counting all electrons for C—C and C—H bonds as we did with saturated hydrocarbons (page 69). The carboxyl group is ignored in the calculation (Kharasch method).

### STRUCTURE OF ACETIC ACID

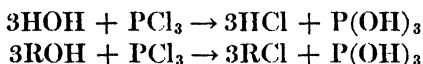
The structure of acetic acid follows from a consideration of analytical data and chemical reactions. The compound has the molecular formula  $\text{C}_2\text{H}_4\text{O}_2$ .

One and only one of its hydrogens is replaceable by sodium to form a salt; this gives us  $\text{C}_2\text{H}_3\text{O}_2$  and H.

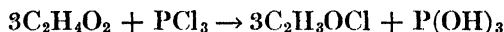
The three remaining hydrogens may be replaced by chlorine or bromine atoms. This reaction, typical of methane and its congeners, seems to indicate the presence of a methyl group.

Now we may obtain acetic acid through the hydrolysis of methyl cyanide,  $\text{CH}_3\text{CN}$ , or through oxidation of acetaldehyde,  $\text{CH}_3\text{CHO}$ . Furthermore when we heat sodium acetate with soda lime we get methane. These reactions, which involve the *formation of the compound and its degradation* all lead to the same conclusion: acetic acid contains the methyl group. We are also assured that acetic acid has a C—C group.

When  $\text{PCl}_3$  reacts with water,  $\text{P}(\text{OH})_3$  is formed and Cl replaces the OH group of water. The same type of reaction occurs when this reagent is used with an alcohol, i.e., OH is replaced by Cl.



Now, when acetic acid reacts with  $\text{PCl}_3$ , we again have O and H simultaneously removed and Cl left in their place:



This reaction proves the presence of an OH group in acetic acid, which is confirmed by other reactions besides that with sodium listed above. The formula is now complete to the extent shown below:

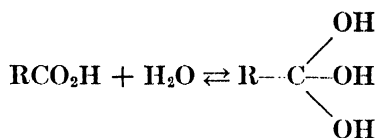
$\text{CH}_3-\overset{\text{O}}{\underset{\text{||}}{\text{C}}}-\text{OH}$ . The remaining oxygen apparently belongs on the carbon atom which holds the hydroxyl group. Thus we come to the formula commonly used. The structure of other acids has been worked out in a

manner similar to the above. While the formula  $\text{RC}-\overset{\text{O}}{\underset{\text{||}}{\text{OH}}}$  is ordinarily used for the fatty acids it does not give complete satisfaction. These acids are associated. This is part of the reason for their high boiling points mentioned before, and the association must occur between carboxyl groups, no doubt causing some alteration in the electronic structure. Physical data (absorption spectra) are quite different for free acids and certain acid derivatives (esters). As the esters are non-associated (low-boiling) compounds, it again seems unlikely that the free acids can have an arrangement of carbon and oxygen just like that of the esters.

In a case of this kind chemists continue to seek diligently for a formula which will typify truly all of the chemical behavior of a compound, but meanwhile use a formula best adapted to show most of the salient facts. For acids this has the carboxyl group. Very likely many of the "reactive molecules" in a sample of an acid actually have the arrangement shown in

$\text{R}-\overset{\text{O}}{\underset{\text{||}}{\text{C}}}-\text{OH}$ . Others may assume this arrangement at the moment of reaction.

We may also suppose that an acid in water solution adds water as shown below:



A reaction of this kind has been shown to occur with aldehydes. The synthesis of derivatives of formula  $\text{RC}(\text{OR})_3$  shows that this polyhydroxy compound is at least capable of existence and at any rate justifies the use of the carboxyl formula for a "reacting molecule." The formula for the associated acid is discussed later (page 174).

### ORTHO ACIDS

The compound of formula  $\text{HC}(\text{OH})_3$  is called orthoformic acid;  $\text{CH}_3\text{C}(\text{OH})_3$  is called orthoacetic acid. Orthoformic acid might be made by the hydrolysis of chloroform; however this reaction actually gives formic acid and water (see equation, page 175), presumably because of the instability of the ortho acid.

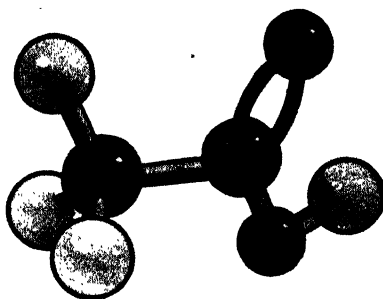
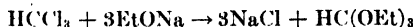


FIG. 29.—Model of acetic acid molecule.



The alkyl derivatives of ortho acids are known; these are called ortho esters. The following equation shows preparation of ethyl orthoformate from chloroform and sodium ethoxide:

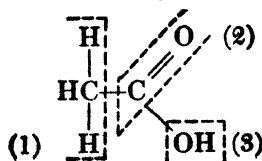


Ortho esters hydrolyze easily in presence of acids; bases do not catalyze the hydrolysis.

### FUNCTIONAL GROUPS OF ACIDS

In previous pages, it has several times been intimated that the groups in organic molecules tend to preserve their typical reactions in the various compounds in which they occur. These separate groups are often called functions, e.g., the carbonyl function, hydroxyl function, etc. In general, as stated above, a functional group will preserve some of its independent reactions in any compound in which it may be found. Thus, whatever is known of the reactions of these groups, may be applied at once to *predict the reactions of new compounds*.

To consider the reactions possible to acetic acid, we might therefore divide it into its component parts or groups as indicated in the diagram herewith:



We find the alkyl group\* (1), the carbonyl group (2), and the hydroxyl group (3). Group (1) may be expected to behave like a saturated hydrocarbon, and the reaction with chlorine shown on page 166 might have been predicted on this basis.

The carbonyl group (2) should absorb polar compounds (as was learned in the study of aldehydes and ketones). In some of the reactions of acids, this appears to be the case (see page 227). However, some of the absorptions shown by aldehydes and ketones do not take place with acids (they do not for instance, form oximes, cyanohydrins, or bisulfite compounds). In other words, the carbonyl group (2) is affected by its environment and behaves in slightly different fashion when hydroxyl group is joined to it.

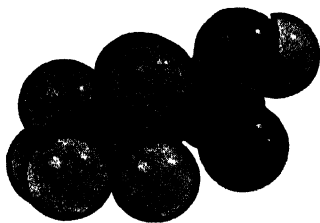


FIG. 30.—Model of butyric acid molecule.

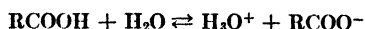
In applying the above theory of functions to the hydroxyl group (3) of an acid, differences are at once seen between this group and the hydroxyl of an alcohol. These are, however, differences of degree and not of kind. The hydroxyl group is found to be more active in an acid than in an alcohol. It behaves like that in an inorganic acid ( $\text{HONO}_2$  or  $(\text{HO})_2\text{SO}_2$

for instance). Its hydrogen is replaced by metals to form salts, and solutions of the fatty acids affect indicators and in other ways show the presence of  $\text{H}^+$  ion. Most of these acids save formic, the first of the series, are very weak as is shown by the ionization constants which follow. The value for carbonic acid is added for comparison.

TABLE 15.—IONIZATION CONSTANTS OF MONOCARBOXYLIC ACIDS

	$T = 25^\circ$	$100 \times K^\dagger$
Formic acid.....		0.01712
Acetic acid.....		0.00175
Propionic acid.....		0.00133
Butyric acid.....		0.00150
Valeric acid.....		0.00138
Caproic acid.....		0.00132
Enanthic acid.....		0.00128
Carbonic acid		
$K_1$ .....		0.00003
$K_2$ .....		$6 \times 10^{-9}$

† A carboxylic acid in water ionizes to give hydrogen ion and the organic anion:



The equilibrium constant for the ionization ( $K_a$ ) is obtained by using the law of chemical equilibrium (see general chemistry text):

$$K_a = \frac{[\text{H}_3\text{O}^+][\text{RCOO}^-]}{[\text{RCOOH}][\text{H}_2\text{O}]}$$

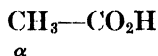
In dilute solutions the concentration of the water may be ignored. This gives:

$$K_a = \frac{[\text{H}_3\text{O}^+][\text{RCOO}^-]}{[\text{RCOOH}]}$$

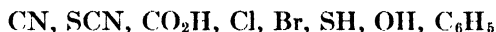
\* See footnote, page 75.

## STRENGTH OF ORGANIC ACIDS

If alkyl hydrogen of a fatty acid is replaced by a negative atom or group, the percentage of ionization (strength of the acid) is increased. The effect is greatest when substitution is on the carbon next to the carbonyl group, the *alpha* carbon atom.

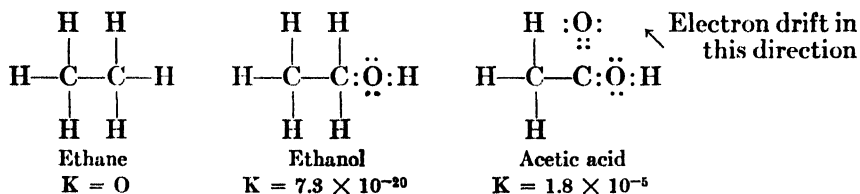


If the group be shifted to the next carbon ( $\beta$ , *beta*) the ionization constant of the acid decreases considerably as will be seen in the following table of values. The effect upon ionization increases as one, two, or three hydrogens are replaced. Certain groups seem to be more "negative" than others and produce a greater effect wherever substituted. A partial list of these groups, written with the more "negative" first is shown herewith:



Positive groups substituted as mentioned above slightly decrease the strength of an acid. See the table on page 172 for the effect of substitutions of this kind on the strength of acids. This subject will be discussed again in later chapters.

A reasonable explanation for the ionization of these acids follows the study of their structures. Consider the three compounds, ethane, ethanol, and acetic acid. None of the hydrogens of ethane is ionizable.



In the alcohol the oxygen has a greater share in the electron pair bonding it to hydrogen than has carbon in ethane. This is due to the highly negative nature of oxygen, which holds its octet of electrons firmly and closely. In consequence the hydrogen is less strongly held and some ionization is noted.

The presence of the second oxygen in acetic acid causes a general drift of electrons in its direction, leaving the hydrogen still less strongly bound, giving this compound a yet higher percentage of ionization. Now if a negative atom such as chlorine be substituted for a hydrogen of the methyl group, the bonding electrons at this point will move outwards toward the

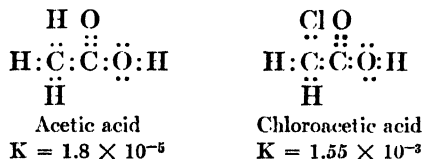


TABLE 16.—IONIZATION CONSTANTS OF SUBSTITUTED ACIDS

	T = 25°	100 × K
Acetic acid,* CH <sub>3</sub> CO <sub>2</sub> H.....		0.00175
Phenylacetic acid, (C <sub>6</sub> H <sub>5</sub> )CH <sub>2</sub> CO <sub>2</sub> H.....		0.00488
Glycolic acid, (HO)CH <sub>2</sub> CO <sub>2</sub> H.....		0.0150
Thioglycolic acid, (HS)CH <sub>2</sub> CO <sub>2</sub> H.....		0.0285
Monobromoacetic acid, (Br)CH <sub>2</sub> CO <sub>2</sub> H.....		0.138
Monochloroacetic acid, (Cl)CH <sub>2</sub> CO <sub>2</sub> H.....		0.155
Dichloroacetic acid, (Cl <sub>2</sub> )CHCO <sub>2</sub> H.....		5.144
Trichloroacetic acid, (Cl <sub>3</sub> )CCO <sub>2</sub> H.....		120.00
α-Chloropropionic acid, CH <sub>3</sub> CHClCO <sub>2</sub> H.....		0.147
β-Chloropropionic acid, ClCH <sub>2</sub> CH <sub>2</sub> CO <sub>2</sub> H.....		0.0086
Malonic acid, (CO <sub>2</sub> H)CH <sub>2</sub> CO <sub>2</sub> H.....		0.160
Thiocyanoacetic acid, (SCN)CH <sub>2</sub> CO <sub>2</sub> H.....		0.260
Cyanoacetic acid, (CN)CH <sub>2</sub> CO <sub>2</sub> H.....		0.365
Methylacetic acid, (CH <sub>3</sub> )CH <sub>2</sub> CO <sub>2</sub> H.....		0.0013
Dimethylacetic acid, (CH <sub>3</sub> ) <sub>2</sub> CHCO <sub>2</sub> H.....		0.0014
Trimethylacetic acid, (CH <sub>3</sub> ) <sub>3</sub> CCO <sub>2</sub> H.....		0.00096

\* The ionization constant of deuterioacetic acid will be of interest. For CH<sub>3</sub>CO<sub>2</sub>D, K = 0.45 – 0.59 × 10<sup>-5</sup>.

chlorine nucleus. This effect is transmitted through the molecule causing a general drift of electrons away from the hydrogen of the OH group.



Substitution of a second and a third chlorine atom would in the same way cause still higher constants of ionization. The effect upon ionizable hydrogen would naturally be less if the chlorine were at a greater distance from the carboxyl group, as was noted with the β-chloropropionic acid.

This outward shift of bonding electrons away from a carbon nucleus is properly considered as a partial oxidation of the carbon (oxidation = removal of electrons). In the light of the theory presented here it is easy to see why the further oxidation of ethanol should affect the carbon already oxidized rather than the other carbon (see page 103). The bonding electrons here have drifted away from hydrogen, due to a general shift towards the oxygen atom, and the two hydrogen atoms on this carbon are less strongly held than are those of the methyl group.

Resuming the discussion begun on page 165, it may be said that the reactions shown by which the acid derivatives and substituted acids are formed are all quite normal for the functional groups found in the fatty acids. As these various compounds are taken up in ensuing sections, the student should look for and note the recurrence of the typical reactions of groups, which have already been learned while studying the alcohols, aldehydes, etc.

## NOMENCLATURE OF ACIDS

The names of several of the fatty acids refer to their natural origin:

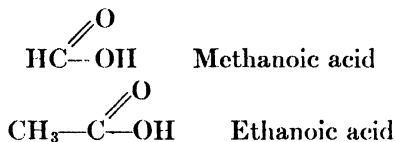
Formic..... from Formica (ant)\*

Butyric..... from butter, . . . etc.

\* A dilute solution of formic acid may be obtained by distilling certain ants with water.

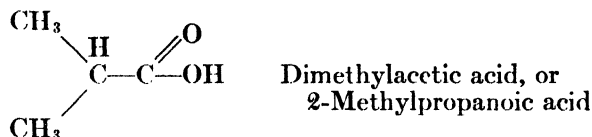
Common names are shown in the table on page 163. The official name is obtained by adding "oic" to the stem name of the hydrocarbon having the same number of carbon atoms.

Examples:



Acids may also be named as derivatives of acetic acid (as alcohols are often named as derivatives of methyl alcohol).

Example:



The concentrated (100%) acetic acid of commerce is called "glacial" acetic acid. Because of its high melting point it is often found in the solid state in which it resembles ice.

## FORMIC ACID

The first member of the series of fatty acids is unique in possessing the properties of both an acid and an aldehyde; inspection of the structure of

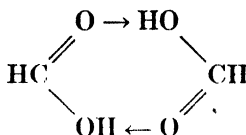
formic acid shows that it can be considered as a fatty acid,  $\text{R}-\text{C}=\text{O}$ ,  $\text{R}-\text{C}-\text{OH}$ ,

having hydrogen in place of the usual alkyl group,  $(\text{H}-\text{C}-\text{OH})$  or as an

aldehyde,  $\text{R}-\text{C}=\text{O}$  having hydroxyl substituted for alkyl  $(\text{HO}-\text{C}-\text{O})$ .

On account of this peculiarity in structure there are corresponding differences in the properties of this acid, which will be noted in a comparison of its reactions and synthesis with those of the higher acids.

It has been shown by the use of a physical method that the formula for formic acid is as follows:



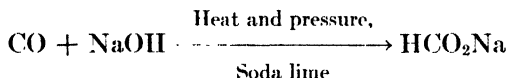
Two molecules are associated and held together by a sharing of electrons, which involves a hydrogen bridge (see page 127). This association, which applies also in the case of acetic acid, is no doubt partially responsible for the high boiling points observed for these compounds. Their chemistry is unaffected, however, since the joined molecules almost certainly separate and act individually in the presence of other reacting molecules.\*

### PREPARATION OF FORMIC ACID

(1) Formic acid, like higher acids, is prepared by the oxidation of the corresponding alcohol:

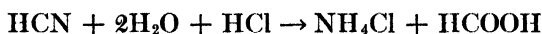


(2) Formic acid is also formed by the union of carbon monoxide and sodium hydroxide:



This reaction is analogous to method (5) on page 164, for the higher acids. **This is the commercial method of preparation**, the acid being liberated from sodium formate by treatment with sulfuric acid.

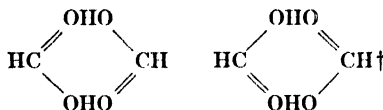
(3) Hydrolysis of hydrogen cyanide yields formic acid:



It is seen that hydrogen cyanide is the nitrile of formic acid. It may be called formonitrile.

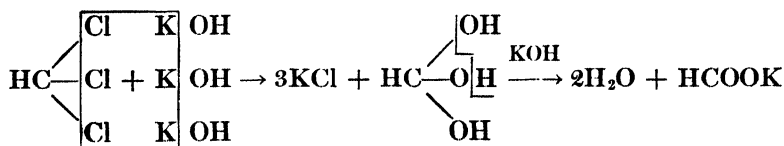
(4) The hydrolysis of chloroform (bromoform or iodoform) will produce formic acid:

\* The formic acid dimer can have two electronic structures as shown below:



† From Taylor and Baker, *Organic Chemistry of Nitrogen*, Clarendon Press, Oxford, 1937.

In these formulas the atoms are in very similar positions but certain electrons have been shifted. The methods of wave mechanics have shown that in cases of this kind we have the phenomenon of resonance. The structure assumed by the molecule is neither of those shown, but a structure intermediate between the two. Resonance will be discussed in more detail later (see page 398).

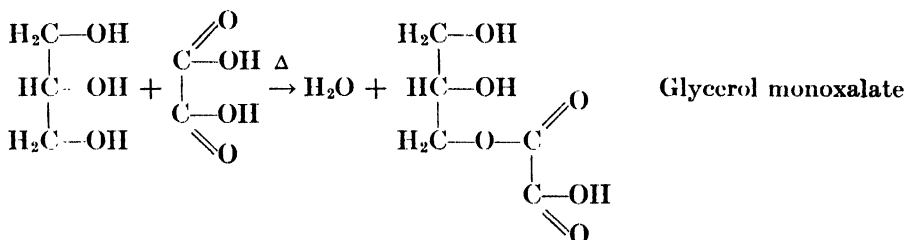


(5) It is also possible to make formic acid from hydrated oxalic acid, employing glycerol as a catalyst:

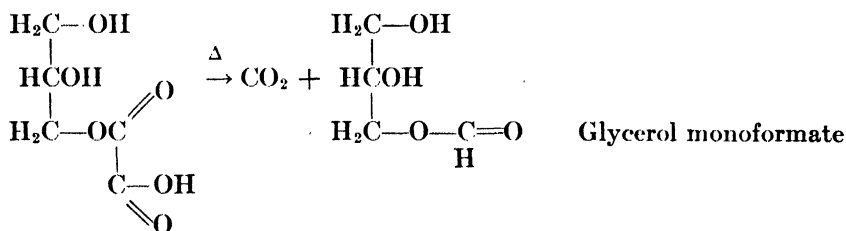


The reaction is supposed to proceed as follows:

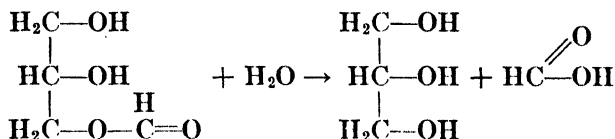
(a) The glycerol is partially esterified by the oxalic acid:



(b) Further heating causes this ester to break down, losing carbon dioxide and thereby producing an ester of formic acid and glycerol:



(c) The formic acid ester of glycerol is hydrolyzed yielding one molecule of formic acid and one molecule of glycerol, which is free to unite with further oxalic acid and produce more formic acid:

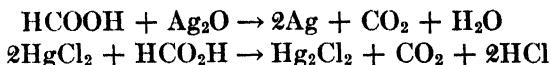


This synthesis of formic acid was frequently used in the past in the laboratory preparation of small amounts of the acid.

#### REACTIONS OF FORMIC ACID

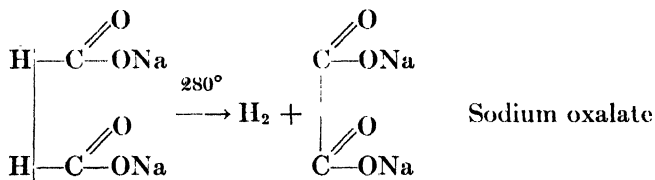
The reactions cited here are those in which formic acid behaves differently from its homologs.

(1) *Oxidation.* Due to its possession of an aldehyde group, formic acid is a strong reducing agent:

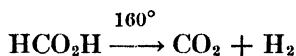


This action is not common to the higher acids. Formic acid readily reduces silver or mercury ion, but acetic acid is so difficult of oxidation that it is frequently used as a solvent in the oxidation of other organic compounds by powerful oxidizing agents.

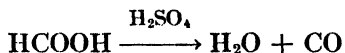
(2) When sodium formate is heated, hydrogen is lost and sodium oxalate results. The synthesis of oxalic acid through use of this reaction is commercially important.



The synthesis of formic acid from oxalic acid has already been indicated. The two compounds are seen to be rather intimately related to each other, each passing easily to the other. Heated alone, formic acid gives hydrogen and carbon dioxide:



(3) *Reaction with concentrated sulfuric acid.* Formic acid treated with a dehydrating agent easily loses the elements of water. Carbon monoxide is produced. The reaction is useful for the preparation of pure CO in small amounts.

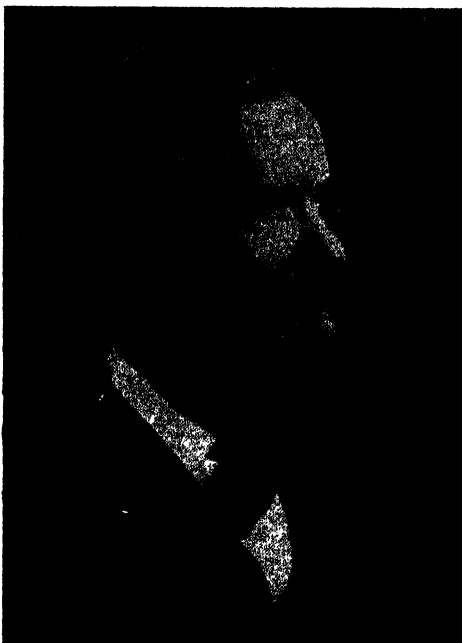


(4) Formic anhydride has so far proved incapable of isolation, whereas anhydrides of the higher acids are readily prepared. For many years it was found impossible to prepare acid halides of formic acid and this was taken as a further instance of peculiarity of this member of the series. Formyl chloride and formyl fluoride have recently been prepared, but are capable of existence only at very low temperatures.

#### SALTS

The monocarboxylic acids, though quite weak in comparison with the mineral acids, are sufficiently strong to decompose carbonates and bicarbonates (see table, page 170). Salts of the organic acids may be made by action of the acids with hydroxides, oxides, carbonates, or bicarbonates of the metals, or in some cases by reaction with the metals.

STANISLAO CANNIZZARO. (1826-1910, Italian.) A noted worker in organic chemistry. He is best known for his work in introducing the Avogadro hypothesis to his scientific colleagues and for the reaction which bears his name. *J. Chem. Soc. (London)*, **101**, 1677 (1912), *J. Chem. Education*, **3**, 1361 (1926), *ibid.*, **4**, 836 (1927); also this book, pages 491, 548.



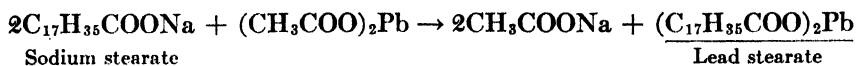
*Journal of Chemical Education.*



FRIEDRICH A. KEKULÉ (von Stradonitz). (1829-1896, German.) Kekulé left the study of architecture for chemistry after hearing Liebig's lectures. He is best known for his structural theories. The introduction of the idea of tetravalent carbon atoms joined to each other was very important for the growth of organic chemical science. The benzene structure of Kekulé was of equal value in stimulating research. Kekulé was author of an unfinished but important textbook of organic chemistry. See *Am. Chem. J.*, **18**, 789 (1896), *J. Am. Chem. Soc.*, **18**, 1107 (1896), *J. Chem. Soc. (London)*, **73**, 97 (1898), *J. Chem. Education*, **4**, 697 (1927); also this book, page 395.

*Journal of the Chemical Society (London).*

Salts which are but slightly water-soluble may be made by double decomposition of soluble salts:



Salts of the alkali metals are water-soluble. Their water solutions are alkaline, due to hydrolysis. Solubility in alcohol is very low; the salts are insoluble in ether.

Although the reactions of the fatty acid salts are presented together with the different compounds to which they give rise, it will serve a useful purpose to collect this material and review it while the subject of acids is before us. Several important types of compounds are formed from the salts of organic acids, as has already been seen. They are:

(1) *The saturated hydrocarbons.* These are formed by heating the sodium salts of fatty acids with excess of a strong base. For equation see page 28. The hydrocarbon formed always has one carbon less than the acid chosen, as one of the carbons is eliminated in the sodium carbonate; in other words, the reaction affords a means of "stepping down" (removing a carbon atom from a normal chain); see page 228.

(2) *The esters.* These compounds result when fatty acid salts react with alkyl halides; for equation see page 203.

(3) *An aldehyde* results when the calcium salt of an acid is heated with calcium formate. The equation is shown on page 137.

(4) *Ketones* form on dry distillation of the calcium salts of acids (page 138).

(5) If the ammonium salt of an acid is heated, water is lost and *an amide* is produced; equation, page 227.

Further dehydration yields a *nitrile* (cyanide); see page 228.

We have seen (page 164) that the addition of water to a nitrile yields its acid; evidently these reactions are reversible.

These examples sufficiently indicate the usefulness of the fatty acid salts in synthetic work. In addition to such employment, specific salts of various acids are used in the arts and in medicine in such numbers that no more can be attempted here than to list a few of the more familiar applications.

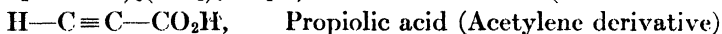
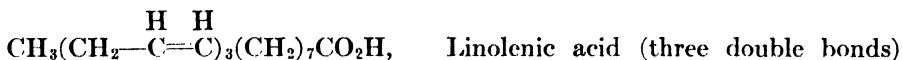
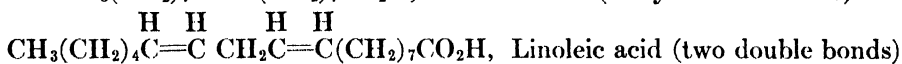
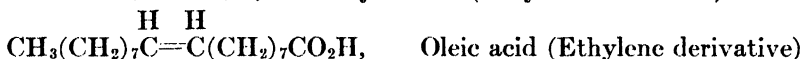
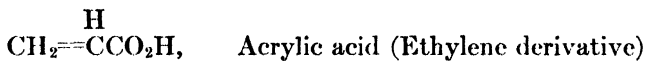
Lead acetate,  $(\text{CH}_3\text{CO}_2)_2\text{Pb} \cdot 3\text{H}_2\text{O}$ , or "Sugar of Lead" is used in medicine, as are also the acetates of zinc and iron. Verdigris,  $\text{Cu}(\text{OH})_2 \cdot (\text{CH}_3\text{CO}_2)_2\text{Cu}$ , a complex of copper acetate and hydroxide, serves as a pigment. "Paris Green" also contains copper acetate; it is an insecticide. Among mordants used in dyeing cloth, we find the acetates of aluminum, chromium, and iron. Mention should also be made of "White Lead," basic lead carbonate, which is formed from lead acetate by the combined action of carbon dioxide and water. The sodium and potassium salts of

acids of high molecular weight are known as soaps. Their reactions and preparation are taken up on page 218.

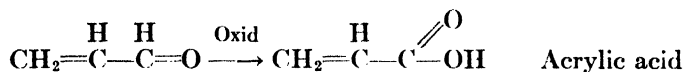
### UNSATURATED MONOCARBOXYLIC ACIDS

These compounds may be viewed as derivatives of ethylene or acetylene, formed by the replacement of hydrogen of such compounds by the carboxyl group. An examination of their structural formulas will readily bear out this conception.

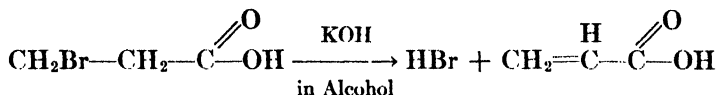
Examples:



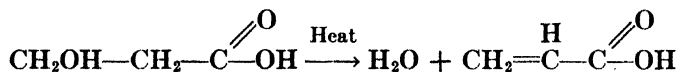
But little further need be said regarding these compounds, as their reactions are a combination of the reactions of saturated acids and of unsaturated hydrocarbons, and can, therefore, be perfectly understood by reference to the chemistry of these two groups. The synthesis of an ethylene acid like acrylic acid may be accomplished by oxidation of the corresponding alcohol or aldehyde, a reaction normally used to produce the saturated acids. Thus acrylic aldehyde on mild oxidation yields acrylic acid:



Another method of synthesis consists in the removal of halogen acid from a halogen-substituted fatty acid (page 235):



or removal of the elements of water from a hydroxy acid:



It will be noticed that the halogen or hydroxyl group to be removed is in the *beta* position, that is on the carbon second removed from the carboxyl group. This is a favorable position for the reactions shown here. Since



both of these methods are described in later sections on substituted acids, they will need no other mention at this time.

Acrylic acid shows a resemblance to ethylene in its ease of polymerization. *Alpha* methylacrylic acid is similar and its methyl ester by polymerization forms valuable resins (Lucite, Plexiglas). These are perfectly colorless resins and for this reason have been proposed for the manufacture of spectacles and other lenses ("non-breakable glass"). Such plastic "glass" because of its transparency and toughness is used in airplane windows (see pages 285, 505).

Oleic and linoleic acids are found as glycerol esters in a number of the natural fats and oils. Both acids have the same carbon skeleton as stearic acid,  $C_{17}H_{35}COOH$ , and on reduction are converted to the latter substance. The position of the double bond in oleic acid is determined by oxidation of the compound. We have found in our study of ethylene compounds that the double bond is sensitive to oxidation; when unsaturated compounds are oxidized, they normally break apart at this point. Oxidation of oleic acid yields two acids each having nine carbon atoms; we therefore know that the double bond is symmetrically placed in the middle of the chain of oleic acid. Treatment of oleic acid with ozone gives confirmatory results. The section on Fats, Oils, Soaps, Waxes will continue the discussion of the unsaturated acids.

Related to the acids discussed here is ricinoleic acid, 12-hydroxyoleic acid,  $CH_2(CH_2)_5CHOHCH_2CH=CH(CH_2)_7COOH$ , produced by the saponification of castor oil. This is used as a plasticizer for artificial leather, as a lubricant, for the synthesis of wetting agents and perfume materials, for preparation of synthetic drying oils.

#### USES OF ACIDS

*Formic acid.* Used as a dehairing agent for hides, in rubber regeneration, in medicine for gout and neuritis, to make esters, as a source material for oxalic acid, as a silvering agent, and in many other ways.

*Acetic acid.* Used as a source material for the derivatives indicated in this and other chapters. Large amounts are used in the preparation of many salts and esters. Cellulose acetate is an important derivative.

Acetic acid, being soluble both in water and in organic liquids, is an excellent solvent. The fact that it resists oxidation and reduction makes it doubly important as a "chemist's solvent." As a weak acid there are many applications. The dilute solution known as vinegar is an important condiment and preservative for foods.

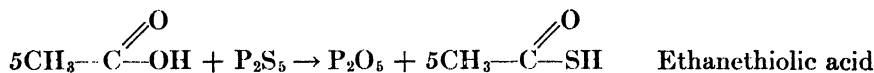
*Higher acids.* Used in synthetic work. Palmitic and stearic acids are used for candles. Their sodium salts are washing soaps, also useful in lubricating mixtures. The acids are used for waterproofing agents, in polishes, cosmetics, and pharmaceutical products. Zinc stearate is used in paints, face powders, enamels, and varnishes. Oleic acid is a waterproofing

agent, is used in leather tanning, for lubricating mixtures, and polishing compounds.

### THIO ACIDS

Organic acids in which sulfur takes the place of oxygen are called thio acids. Three types of these compounds are possible:

(1) Carbothiolic acid,  $\text{R}-\overset{\text{O}}{\parallel}\text{C}-\text{SH}$  (oxygen of hydroxyl group replaced by sulfur). These acids are prepared by the action of phosphorus sulfide on the corresponding oxygen acid:

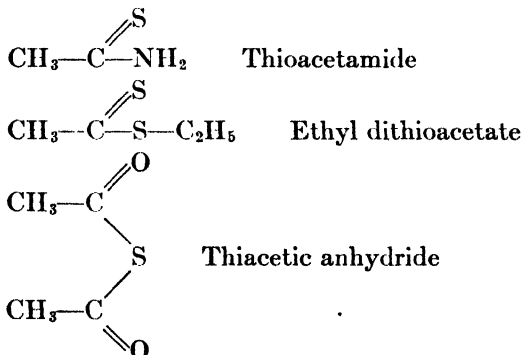


(2) Carbothionic acid,  $\text{RC}=\overset{\text{S}}{\text{OH}}$  (oxygen of carbonyl group replaced by sulfur). These acids do not exist in the free state, but are known in the form of their derivatives.

(3) Dithio- or carbodithiolic acid,  $\text{R}-\overset{\text{S}}{\parallel}\text{C}-\text{SH}$  (all oxygen replaced). These acids may be prepared by the Grignard reaction (page 574).

The thio acids form derivatives which are analogous to those formed by the corresponding oxygen acids.

Examples:



It cannot, however, be said that the chemistry of these acids or their derivatives exactly follows that of the corresponding oxygen compounds, although many points of similarity exist between them. As a general rule the sulfur compounds are less stable than the oxygen derivatives, and for this and other reasons they have not attained an equal importance.

**Digression. Identification of Compounds.** As mentioned in the last chapter, the identification of organic compounds is almost a routine procedure for a research chemist. Practice in identification is useful for



the student as well. We realize quite fully that even an indifferent student can make preparations in the laboratory, or at least some of them, if provided with an adequate manual, and an occasional student will find such work uninteresting because the results are foreseen.

The situation is different when one is given an unknown compound for identification. It is useless to attempt the work unless there is a considerable fund of knowledge of reactions, habits, and properties to be drawn upon. As most of us have the detective instinct, this type of work is usually followed with keen interest. It is preeminently laboratory work, and the methods and details are best left to the special manuals which treat of identification. The reason for bringing it up here is that the first exercises in identification are often carried out at this point in the course, making it desirable to introduce a short résumé which will omit the practical details.

Suppose that the unknown belongs to one of the groups we have had for study (hydrocarbon, halogen compound, alcohol, ether, aldehyde, ketone, acid). Consider first the analysis for elements other than carbon and hydrogen. If halogen is present a compound of the second group is in hand. Consider water-solubility. If the compound, a liquid, is completely water-soluble, it cannot be a hydrocarbon or ether or halogen compound, but it could be an alcohol, aldehyde, ketone, or lower acid. Try reaction of a water solution to litmus paper. Acid reaction here would bar all groups but one. As soon as all but one or two groups have been eliminated in this way, specific tests will decide which group is concerned. We then decide which actual compound we have by a check of boiling point, melting point, density, etc., of the unknown against tables of these values, and, having located our compound in the list, we assure ourselves of its identity by making a solid derivative whose melting point is noted. If we again get a check, the analysis is successfully completed.

Frequently the first laboratory exercises in identification are no more than that the compound should be placed in its proper homologous series through the use of suitable tests and through inspection of physical properties. This type of analysis can be applied to all classes of compounds so far studied, while the preparation of derivatives for some classes (hydrocarbons, halogen compounds, ethers) is not easily carried out.

Lists of derivatives and a summary of information concerning identification will be found in Chapter XI.

### REVIEW QUESTIONS

1. Show by equations the formation of propionic acid from: (a) Ethyl cyanide; (b) Methyl propionate; (c) Potassium propionate; (d) Propyl alcohol.
2. Indicate by equations the reaction of propionic acid with: (a) Sodium; (b) Sodium hydroxide; (c) Propyl alcohol; (d) Phosphorus pentachloride; (e) Phosphorus pentasulfide; (f) Ammonia.
3. Show by a series of equations how acetic acid may be made from methyl alcohol.
4. How could propiolic acid be distinguished from acrylic acid?

5. Show by equations the action of bromine, and of hydrogen iodide, upon acrylic acid.
6. Give two methods of preparation for acrylic acid.
7. Indicate by means of equations, the action of zinc upon  $\alpha$ ,  $\beta$ -dibromopropionic acid; of alcoholic potash upon  $\beta$ -bromobutyric acid.
8. The sodium salt of a certain acid when heated with sodium hydroxide (solid) yields ethane. What acid was used? (Write equation.)
9. How could a solid hydrocarbon be distinguished from a solid fatty acid?
10. How many cc. of normal NaOH solution would be required to neutralize 2.5 grams of acetic acid?
11. A certain monocarboxylic acid was titrated against N/10 KOH solution. A sample weighing 0.2100 g. required 18.10 cc. of the KOH solution. What is the molecular weight of the acid?
12. Write structures of the isomeric acids which have the formula indicated in problem 11. Name each compound.
13. Show by equations the production of acetaldehyde, and of acetone, from acetic acid.
14. How could the presence of formic acid in acetic acid be detected?
15. Name five derivatives of acetic acid with their uses.
16. Give two methods of preparation which are unique for formic acid, i.e., not applicable to higher acids.
17. Show by means of a chart the relationships between methyl alcohol, acetylene, acetic acid, ethyl alcohol, methyl cyanide, methyl iodide, oxalic acid, methane, and ethane.
18. Carbon monoxide is to be transformed to sodium formate, and thence to sodium oxalate. Assuming a 75% yield in each step of the process, how much sodium oxalate will be formed from 40 liters of carbon monoxide?
19. The silver salt of a monocarboxylic acid contains 60.33% Ag. Give the formula of the acid.
20. If the above acid was treated with HI, and the reaction product then treated with sodium methoxide, what substance would result?
- (R)21. Outline methods for making the following compounds. (a)  $\text{BrCH}_2\text{CH}_2\text{CO}_2\text{H}$ ; (b)  $\text{CH}_3\text{CHClCO}_2\text{H}$ .
22. Which types of compounds so far considered in this book are capable of acting as acids? Include all which are even faintly acid.
23. Should methyl alcohol be any more soluble in  $\text{K}_2\text{CO}_3$  solution than in water? Why? Should  $n$ -amyl alcohol (say pentanoic) be any more soluble in  $\text{K}_2\text{CO}_3$  solution than in water? Why?
24. How could you distinguish a liquid fatty acid from a liquid alcohol?
25. Is formic acid commonly made by the oxidation of formaldehyde? Why?
- (R)26. Calculate the heat of combustion of each of the following compounds: butyric acid, acetic acid, caproic acid, diethylacetic acid. Check your answers with a handbook.
27. A viscous, inodorous liquid is completely water-soluble. Is it a fatty acid, saturated or unsaturated?
28. The unknown is a colored liquid, not soluble in water. To what group does it probably belong? What test should be made first?
29. What is a simple test to distinguish a monocarboxylic acid from an aldehyde?
30. A certain liquid was supposed to be an alcohol, since it reacted with Na as alcohols do. It was not oxidized, however, when warmed with sodium dichromate and  $\text{H}_2\text{SO}_4$ . What type of compound might this have been? What further tests should be applied?
31. In what way could a solid acid be distinguished from a solid alcohol?
32. A certain process liberated as by-products a mixture (solution) of fatty acid of boiling point  $160^\circ$ , and acetone. It was desired to recover both products. What suggestions have you to offer?
33. A liquid has a boiling point of  $197^\circ$ . It is completely water-soluble. Can it be a monohydroxy alcohol?

34. A colorless liquid, when treated with  $\text{Na}_2\text{CO}_3$  solution, liberates  $\text{CO}_2$  freely. To what group may it belong?
35. How could metallic Na be used to distinguish between an alcohol and a saturated hydrocarbon?
36. A certain compound, when treated with a solution of  $\text{KMnO}_4$ , is instantly oxidized. Of what value is this test in an identification?
37. A white powder, somewhat soluble in water, when heated, vaporizes easily giving a choking, irritating white vapor. What clue is furnished by this test?
38. A liquid shows acid properties, and when heated with ammoniacal silver nitrate solution, it gives a silver mirror. What is the verdict?
39. Bearing in mind that naturally occurring organic acids have an even number of carbon atoms, can you formulate a theory regarding the method of their formation in the plant (animal)?
- (R)40. Show how to make  $\beta$ -ethylbutyric acid, using ethyl alcohol as a source material for all organic intermediate compounds.
41. When chloroform is warmed with water and Fehling's solution, a precipitate of cuprous oxide is secured. Explain this, with equations.
42. List the reactions of the acids in groups: (a) Those affecting OH group; (b) Those affecting alkyl H atoms; (c) Those affecting the COOH group.
43. The boiling point of ethanol is  $78.5^\circ$ ; that of ethyl iodide is  $72.4^\circ$ . Can you offer an explanation of the apparent anomaly shown in these values?
44. List a series of facts which will serve to establish the structure assigned to propionic acid.
45. Show by the use of equations how to make from acetic acid three different compounds which are used in the practice of medicine.
46. The freezing point constant for acetic acid is 39. What should be the freezing point of acetic acid diluted with 1% of water?
47. Write complete equations for the following conversions.
  - (a) Ethylene (A) + HI  $\rightarrow$  (B);
  - (b) (B) + KCN  $\rightarrow$  (C);
  - NaOH
  - (c) (C) +  $2\text{H}_2\text{O} \longrightarrow$  (D);
  - NaOH
  - (d) (D)  $\xrightarrow{\Delta} \longrightarrow$  (E).

Outline a simple practical method for making (E) from (A).

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## CHAPTER IX

### ACID DERIVATIVES (I)

#### ACYL HALIDES, ACID ANHYDRIDES

The acid derivatives naturally divide themselves into two main groups. The first group consists of the acyl or acid halides and the acid anhydrides, compounds whose reactions yield, in general, the same derivatives as may be obtained by direct use of the acids. They are more reactive than the acids, and hence in many instances more desirable for synthetic work than the acids would be. The anhydrides and acyl halides might be called "laboratory chemicals," as they are almost exclusively used in synthetic and analytical work.

Members of the second group include the salts, the esters, and the amides; these substances result from reactions of acids, anhydrides, or acyl halides. Representatives from the series of salts, esters, and amides find the widest possible use in industry and the arts, and are met with on every hand. They are found in nature while members of the first group are not.

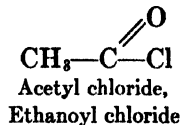
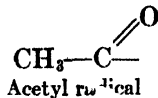
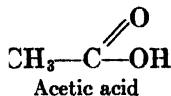
#### ACYL HALIDES

Acyl halides are acid derivatives in which the OH group of the acid has

been replaced by halogen (Cl, Br, I). Their type formula is:  $\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-\text{X}$  (X = Cl, Br, I). The chlorides are by far the most important of the series, being more reactive than the bromides or iodides and less expensive. The only one will be discussed in this book.

The radical  $\text{R}-\overset{\text{O}}{\parallel}{\text{C}}-$  is called an "acyl" radical and for any given acid the name of this radical is obtained by dropping the final "ic" from the name of the acid and adding "yl" in its place.

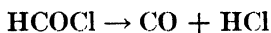
Example:



The acyl radicals must not be confused with the ions of the acids. Compare the structure of the acyl radical shown above with that of the

acetate ion,  $\text{CH}_3\text{CO}_2^-$ . The acyl halides do not ionize, but instead react with water.

The acid chloride of formic acid has not as yet been isolated at room temperature, though there is reason to believe that it exists at very low temperatures. At temperatures above  $-80^\circ\text{C}$ . it appears to decompose rapidly as shown below. Reactions at room temperature, which should yield this compound, give instead carbon monoxide and hydrogen chloride:



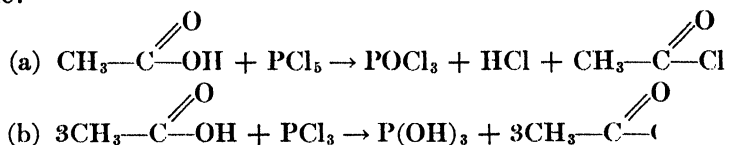
Such a mixture may be used in lieu of formyl chloride in certain reactions (see Chapter XXVIII). In the presence of suitable catalysts the reaction given above is evidently reversible.

This series, therefore, begins with the compound with two carbon atoms, as is the case with certain other series we shall study. Ethanoyl chloride (acetyl chloride),\* is a colorless liquid with a sharp, irritating odor suggesting hydrogen chloride and acetic acid. It fumes when exposed to air, due to reaction with moisture which yields hydrogen chloride. Other acyl halides of low molecular weight have properties similar to those of acetyl chloride; those of high molecular weight are solids.

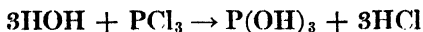
Those acyl chlorides derived from acids soluble in water dissolve in water by reason of their hydrolysis, though as a class the acid chlorides are not water-soluble. The table on page 230 will show that the acid chlorides have boiling points lower than those of the acids from which they are made.

#### PREPARATION OF ACID CHLORIDES

(1) They may be made from the corresponding acid and phosphorus chloride:



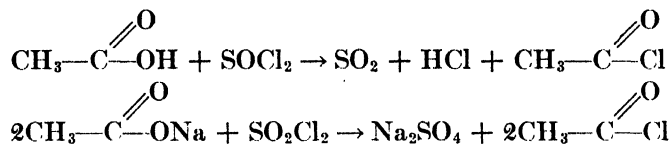
This equation (b) shows only one of the ways in which the substances can interact. Other reactions yield HCl and acid organic derivatives of phosphorous acid respectively. Note the analogy of the reaction shown here and that of alcohol (or water) and halide:



\* The I.U.C. system of naming acid chlorides adds "oyl" to the stem name of the parent hydrocarbon. Since these names are not yet in common use, the older names will be used along with the new in this book.



(2) Preparation from an acid and thionyl chloride or sulfuryl chloride:



The second equation above shows the **commercial method for making acetyl chloride**. The sulfuryl chloride is prepared by direct union of chlorine and sulfur dioxide.

(3) Preparation from the salt of an acid and phosphorus oxychloride:

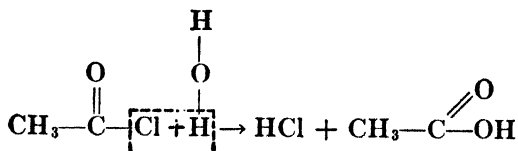


(4) It is possible to make the lower more volatile acid chlorides by treatment of the organic acid with a high-boiling acid chloride. Benzoyl chloride and phthaloyl chloride have been used in this way in methods recently perfected. (See articles by Kyrides, *J. Am. Chem. Soc.*, **59**, 206 (1937), and by Brown, *J. Am. Chem. Soc.*, **60**, 1325 (1938).)

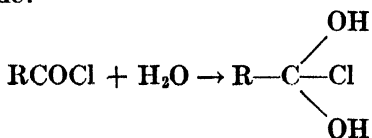
### REACTIONS OF ACID CHLORIDES

Acyl halides may be looked upon as mixed anhydrides of inorganic and organic acids. They are extremely reactive substances. Halogen attached to acyl radical is much more loosely held than in an alkyl halide. Therefore we find the acyl halides taking part in a number of important metathetical reactions, the products of which are well known and useful.

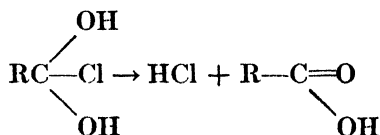
(1) *Action of water.* Considering the acyl halide as a mixed anhydride we see that water acts to regenerate the original acids. This hydrolysis is quite violent when the organic acid concerned is soluble in water.



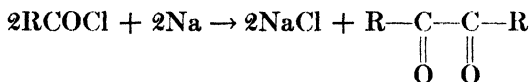
likely that in this reaction water first adds to the carbonyl acid halide:



after which the intermediate compound loses hydrogen chloride:

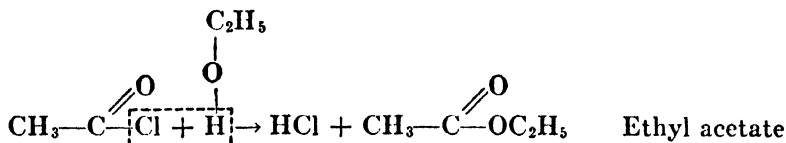


If the reaction simply involved metathesis as diagrammed above, we should also expect such a reaction as the following to occur:



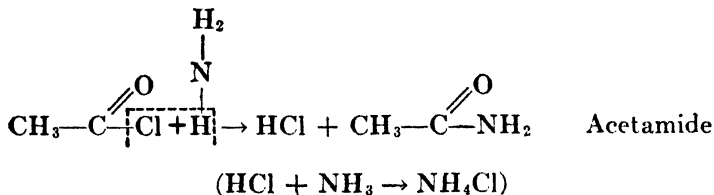
However this reaction does not take place.\*

(2) *Reaction with alcohols.* This reaction, as would be expected, is quite analogous to hydrolysis, since alcohols are water-type compounds (see page 805).



This is a method of ester formation (esterification), called "acetylation," useful for the detection and estimation of OH groups in organic compounds.

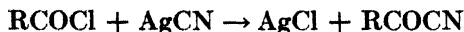
(3) *Reaction with ammonia;* formation of amides (page 227).



The diagrammatic presentation given in these three cases does not show the mechanism of reaction, which is probably the same for all three, and is explained under (1).

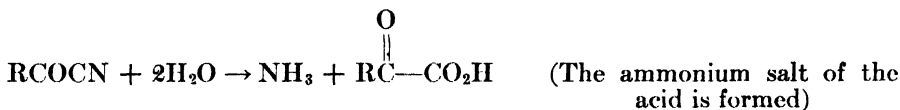
It will be noted that in each of these examples the by-product is a gas; it is removed from competition by side-reactions. For this reason the reactions shown tend to go to completion and the yields are good. This advantage is partly offset by the higher price of acyl halides as compared with acids.

(4) *Acyl cyanides* are produced by reaction with silver or mercury cyanide:



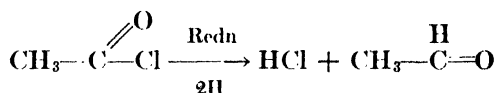
\* It is possible that such compounds are formed as intermediates in the reaction of high molecular weight acid chlorides and sodium.

We have seen that a nitrile upon hydrolysis gives an acid. The acid (acyl) nitrile, or acyl cyanide, gives an *alpha* keto acid:



(5) *Reaction with salts of fatty acids.* Acid anhydrides are formed. The equation is shown in the section on anhydrides (page 191).

(6) The catalytic reduction of an acid chloride leads to the production of the corresponding *aldehyde*. An acid chloride might be considered as a substitution product of an aldehyde. In some cases acid chlorides are actually made from the aldehydes (see page 523).



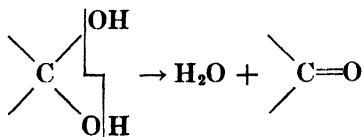
The direct reduction of acids to aldehydes is in general not a practical measure. Instead we reduce their acid halides, or in some cases their anhydrides, esters, or other derivatives.

(7) Acid chlorides may be used to form *ketones* by the Friedel and Crafts reaction (page 578).

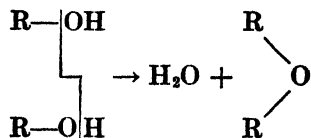
**Phosgene, or Carbonyl chloride,  $\text{COCl}_2$ ,** the acid chloride of carbonic acid, is formed by union of carbon monoxide and chlorine, or from the oxidation of chloroform (see page 260). Its reactions are similar to those of other acid chlorides.

#### ACID ANHYDRIDES

In the study of aldehydes we have found that when two OH groups join to one carbon atom, water is lost between them (page 141).

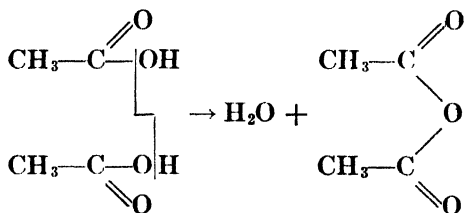


Similarly two molecules of alcohol type may lose water coöperatively:

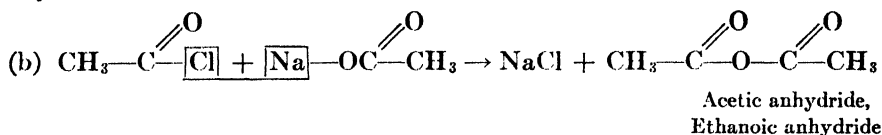


In this way the ethers are formed. These examples make it seem possible that any two molecules containing OH group may undergo this kind of reaction which, with certain limitations, is the fact.

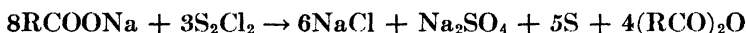
**Preparation.** (a) When two molecules of an organic acid react so as to lose water between the two OH groups, the compound formed is called an acid anhydride:



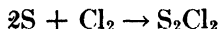
Ordinarily the reaction is not carried out between molecules of the acid itself,\* but the anhydrides are made from an acid chloride and the salt of a fatty acid:



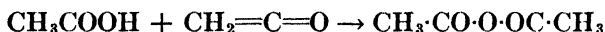
**A commercial method** uses the reaction of the salt of an organic acid with sulfur monochloride,  $\text{S}_2\text{Cl}_2$ .



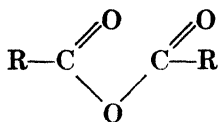
The sulfur may be converted to sulfur chloride and utilized in the main reaction if chlorine is passed into the reaction mixture:



**A commercial method** for the preparation of acetic anhydride involves heat treatment of ethylidene diacetate (page 204). This gives the anhydride and acetaldehyde. **Another commercial method** uses acetic acid and ketene (page 290):



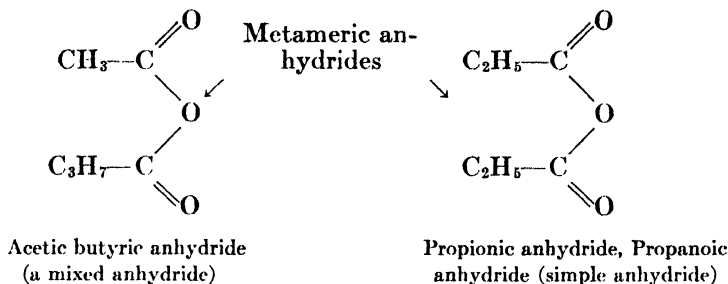
The reaction (b) shown above is analogous to the Williamson reaction for making an ether. As the ethers may be called alkyl oxides, so it is possible to consider the acid anhydrides as acyl oxides. They have the type formula:



(c) If the acid chloride of one acid is put into reaction with the salt of another acid, a *mixed anhydride* results. An example of such a compound is

\* Acetic anhydride may be made in about 50% yield by passing the vapors of acetic acid over a special catalyst at 600°C.

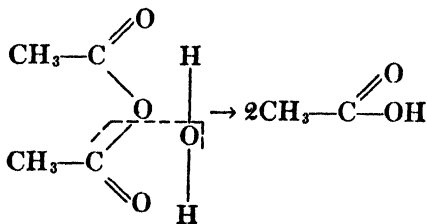
shown below together with a *simple anhydride* of the same molecular formula, to illustrate the metamerism which exists in this series of compounds.



The series of acid anhydrides begins with acetic anhydride, as formic anhydride has not so far proved capable of preparation. Acetic anhydride is a colorless liquid with a somewhat disagreeable piercing odor. It is slightly soluble in cold water, in which the higher anhydrides are insoluble. By reference to the table, page 230, it is seen that acid anhydrides have boiling points higher than those of the acids from which they are made.

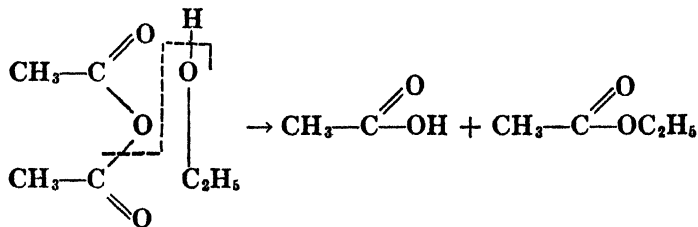
#### REACTIONS OF ACID ANHYDRIDES

(1) *Reaction with water, hydrolysis.* By such action the anhydride is decomposed into the acids from which it was originally formed:

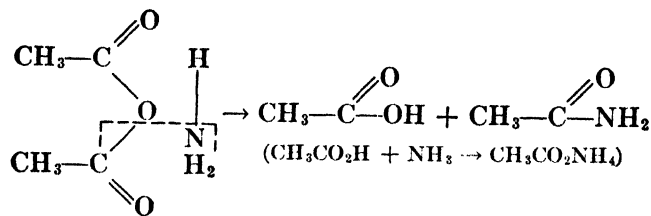


This reaction which proceeds rapidly between warm water and acetic anhydride is effected with greater difficulty with anhydrides of higher molecular weight. It is, however, easily carried out by the use of solutions of the strong bases.

(2) *Reaction with alcohols.* This reaction is similar to that with water and may be called *alcoholysis*. Esters are produced in this manner:



(3) *Reaction with ammonia.* This again is similar in type to the reaction with water. It may be termed *ammonolysis*.



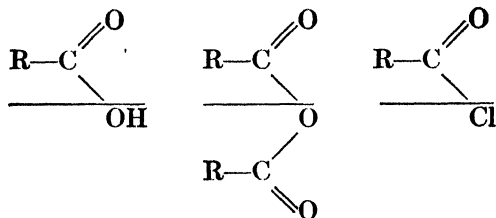
This reaction serves for the preparation of amides.

The above reactions show how acid anhydrides serve for the detection of the hydroxyl or amino group. They are frequently so used as "acylating agents" (as are the acid chlorides) qualitatively to show the presence of such groups, and also in a quantitative manner when one wishes to estimate the number of hydroxyl groups in a compound.

In one practical method the unknown is treated with a solution of excess acetic anhydride or acetyl chloride in pyridine. When reaction has been completed (acetyl chloride reacts more rapidly of the two) the acetylated compound is collected and purified. It is then hydrolyzed in the presence of an excess of standard base; the amount of acid released in the hydrolysis is obtained from a back titration with standard acid.

The anhydrides of dicarboxylic acids are considered on page 254.

**Comparison of Acid, Acid anhydride, and Acid chloride.**



The similarity of structure displayed by acid, anhydride, and acid halide corresponds to the fact that their main reactions are also alike. In any given case the acid is likely to be least reactive, and the halide most reactive.

When an acid forms a derivative, water is usually the by-product. The acid anhydride gives a mole of its organic acid as by-product, while the acid chloride yields HCl gas as by-product.

#### USES OF ACYL HALIDES AND ACID ANHYDRIDES

Both types, especially the acetyl compounds, are used to introduce the acetyl group into organic compounds (acetylating agents).\* The treat-

\* Acylation refers to a treatment which introduces an acyl group. When the acetyl group is introduced, the process is called acetylation.

ment of cotton with acetic anhydride, catalyzed by sulfuric acid, gives cellulose acetate, important for manufacture of a type of Rayon and for making acetate photographic film (non-inflammable). The presence of OH and  $\text{NH}_2$  groups in compounds may be detected and the number of such groups estimated by the use of these reagents, as stated before. For data regarding the use of acetamide as an acetylating agent, see page 229.

**Digression. Types of Anhydrides.** All of the substances treated in this chapter are actually anhydrides. To bring out this fact they are classified below:

Type	Example
Anhydrides of organic acids	
Simple.....	Acetic anhydride
Mixed.....	Acetic propionic anhydride
Anhydrides of organic and halogen acids....	Acetyl chloride
Anhydrides of organic acids and inorganic hydroxy acids.	Acetyl sulfate, $\text{CH}_3\text{CO}(\text{OSO}_3\text{H})$ , acetyl nitrite, $\text{CH}_3\text{CO}(\text{ONO})$ , and acetyl nitrate, $\text{CH}_3\text{CO}(\text{ONO}_2)$ . The latter substance is an excellent nitrating agent.

TABLE 17.—ACID CHLORIDES AND ACID ANHYDRIDES

Name	Formula	M.p., °C.	B.p., °C.	Sp. g., 20°/4°	Ht. of comb.
Acetyl chloride.....	$\text{CH}_3\text{COCl}$	-112.0	+ 52.0	1.104	
Propionyl chloride.....	$\text{C}_2\text{H}_5\text{COCl}$	- 94.0	80	1.065	
Butyryl chloride.....	$\text{C}_3\text{H}_7\text{COCl}$	- 89.0	102.0	1.028	
Isobutyryl chloride.....	$(\text{CH}_3)_2\text{CHCOCl}$	- 90.0	92.0	1.017	
Valeryl chloride.....	$\text{C}_4\text{H}_9\text{COCl}$	.....	127-8	1.016 <sup>15</sup>	
Isovaleryl chloride.....	$(\text{CH}_3)_2\text{CHCH}_2\text{COCl}$	.....	113.5	0.989	
Caproyl chloride.....	$\text{C}_5\text{H}_{11}\text{COCl}$	.....	153.0 <sup>738</sup>		
Capryl chloride.....	$\text{C}_7\text{H}_{15}\text{COCl}$	.....	195.0	0.975 <sup>8</sup>	
Acetic anhydride.....	$(\text{CH}_3\text{CO})_2\text{O}$	- 73.0	139.6	1.082	432
Propionic anhydride.....	$(\text{C}_2\text{H}_5\text{CO})_2\text{O}$	- 45.0	168 <sup>780</sup>	1.012	747
Butyric anhydride.....	$(\text{C}_3\text{H}_7\text{CO})_2\text{O}$	- 75.0	198.2	0.978 <sup>15.5</sup>	
Isobutyric anhydride.....	$[(\text{CH}_3)_2\text{CHCO}]_2\text{O}$	- 53.5	182.5	0.950 <sup>25</sup>	
Valeric anhydride.....	$(\text{C}_4\text{H}_9\text{CO})_2\text{O}$	.....	218.0	0.922 <sup>17</sup>	
Heptylic anhydride.....	$(\text{C}_6\text{H}_{13}\text{CO})_2\text{O}$	+ 17.0	258-268	0.932	1985

### REVIEW QUESTIONS

1. Write the formula for the butyryl radical, and for the amide, ethyl ester, and calcium salt of butyric acid.
2. In what general sense do acyl halides and acid anhydrides differ from esters, amides, and salts? Are representatives of the first two classes found in nature?
3. Write equations for two methods of preparation of propionyl chloride.
4. Show by equations the reaction of propionyl chloride and: (a) Water; (b) NaOH solution; (c) Ammonia; (d) Methyl alcohol; (e) Sodium acetate; (f) Ethylene glycol.
5. Give equation for the preparation of propionic anhydride.

6. Write equations for the action of: (a) Water; (b) Ethyl alcohol; (c) Ammonia; upon propionic anhydride.
7. Outline the tests by which an organic acid may be distinguished from: (a) An acid anhydride; (b) An acyl halide.
8. A certain monohydroxy alcohol gave by reaction with acetyl chloride the compound  $C_3H_6O_2$ . What alcohol was used?
9. Calculation shows that a gram-molecular weight of a certain alcohol required 78 g. of acetyl chloride for complete reaction. How many OH groups are contained in this alcohol?
10. By what chemical tests could acetyl chloride be distinguished from propyl chloride?
11. A compound whose molecular formula is  $C_3H_8O_2$  was converted to a compound of formula  $C_7H_{12}O_4$  by treatment with acetyl chloride. How many OH groups were present in the original compound?
12. Write equation for the action of acetic anhydride upon the compound of problem 11.
13. Show the probable mechanism of the reaction between water and acetic anhydride.
14. An acyl halide may be prepared from an acid by the use of  $PCl_3$  or  $SOCl_2$ . Do you see any advantage in the use of the latter substance?
15. Upon what basis may  $RCOCl$  compounds be classed as acid anhydrides? What reactions support this conception?
16. Acetyl chloride was treated in separate tests with the following reagents: ether, sodium in benzene, ethyl alcohol, formic acid, acetic acid. In which cases did a reaction occur? Write equations for possible reactions.
17. What outstanding physical and chemical properties aid in the identification of an acid chloride?
18. What derivative of acid chlorides and acid anhydrides mentioned in this chapter would in your opinion be suitable as an identification compound for a given acid chloride or anhydride?
19. In case an acid will not form an ester with a given alcohol (and sulfuric acid) or will not easily do so, what other method of procedure might be tried?
20. A certain weight of acetic acid contains 10% of water. What relative weight of acetic anhydride should be added so that upon its hydrolysis the acetic acid concentration will be 100%?
21. Devise a method of analysis to ascertain the amount of acetic acid in a solution of acetic acid and acetic anhydride.
22. What reactions cited in this chapter may be used to prove the structure of acetic anhydride?
23. Complete the following equations.
  - (a)  $CH_3COONa + C_2H_5COCl \rightarrow$
  - (b)  $ClCH_2CH_2COCl + H_2O \rightarrow$
  - (c)  $C_2H_5COCl + RNH_2 \rightarrow$
  - (d)  $C_2H_5COOCOC_3H_7 + H_2O \rightarrow$
24. Name the following formulas.
  - (a)  $CH_3CHClCH(CH_3)CH_3$ ; (b)  $(CH_3)_2CHCH_2COCl$ ;
  - (c)  $CH_3CHClCH_2COCl$ ; (d)  $BrCH_2COCl$ .
- (R)25. The three compounds (A), (B), and (C) have the same vapor density, 44 ( $H_2 = 1$ ), and the same molecular formula. Analysis of (A) gave these results: a sample weighing 0.180 g. gave 0.360 g. of  $CO_2$  and 0.1463 g. of  $H_2O$ . When (A) was warmed with an excess of NaOH solution, the sodium salt of an acid (D) was formed, and a liquid (E). (E) with acetyl chloride gives (F) whose molecular formula is  $C_8H_{10}O_2$ . The sodium salt of (D) reacted with an excess of concentrated sulfuric acid, liberating a gas which burned with a bright blue flame.  
When (B) was warmed with an excess of NaOH solution the sodium salt (G) was produced and a liquid (H) which gave a positive iodoform test and which upon reaction with propionyl chloride gave a compound of formula  $C_8H_{10}O_2$ .



When (G) was heated with concentrated sulfuric acid an acidic liquid was obtained. Its analysis led to these results: C, 40.00%, H, 6.67%. The molecular weight was 60. (C) reacts with NaOH solution to give a sodium salt containing 20.92% Na. No other organic product is secured. Prove the structures of (A), (B), and (C), and explain the reactions discussed in the problem.

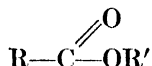
26. A compound (A) with molecular formula  $C_3H_8O_2$  was treated with an excess of acetic anhydride. The resulting acetate (B) was hydrolyzed. Hydrolysis of 0.20 g. of (B) gave an amount of acetic acid requiring 27.20 cc. of 0.092N NaOH solution for its neutralization. How many hydroxyl groups are present in (A)?

## CHAPTER X

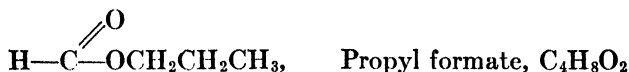
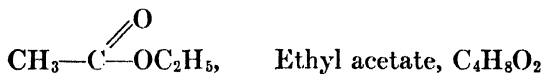
### ACID DERIVATIVES (II)

#### ESTERS AND RELATED COMPOUNDS

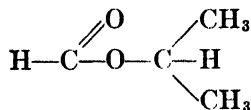
**Introduction.** Esters are acid derivatives which, like the salts, are made by replacement of the hydrogen of the hydroxyl group. In the salts a metal replaces this hydrogen while in the esters replacement is by a hydrocarbon group. The type formula of an ester of an organic acid is therefore:



R and R' in this formula may be identical or different; this introduces a new type of metamerism which is illustrated by the following examples of esters having the same molecular formula, but derived from different acids, with different hydrocarbon groups in place of hydrogen:

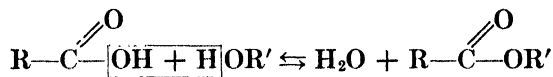


Further isomerism is possible because, both R and R' being hydrocarbon groups, they may exhibit the structural isomerism of the saturated hydrocarbons. In the present case this adds



isopropyl formate, to the list of isomeric esters having the molecular formula  $\text{C}_4\text{H}_8\text{O}_2$ .

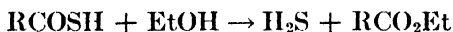
**Formation of Esters.** Both the organic and inorganic acids form esters. The physical properties of the former show greater similarity than those of the latter, since the organic acids are a homogeneous group while the inorganic acids differ widely among themselves. However, in all cases an ester is formed by reaction of an acid with an alcohol, in which water is lost between the hydroxyl groups of the two:



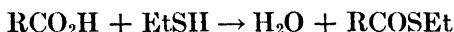
Through this reaction or others derived from it, the alkyl group of the alcohol is substituted for hydrogen of the acid.\*

The equation above has been written so as to show loss of hydrogen by the alcohol and hydroxyl by the acid, which in the light of ionization data for acids and alcohols may seem strange. The reaction is not ionic, however, and is not to be compared with the neutralization of an acid by a base.

When a sulfur acid and oxygen alcohol interact an oxygen ester forms:

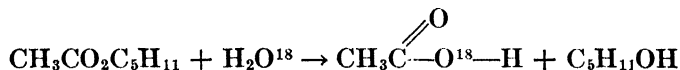


but when an oxygen acid and sulfur alcohol act upon each other we get a sulfur-containing ester:



As the hydrogen comes from the alcohol and hydroxyl from the acid in this case, we feel assured that the same thing happens when an oxygen acid and oxygen alcohol react. Absolute proof of the validity of our assumption has been given by experiments in esterification of alcohols and hydrolysis of esters, using heavy oxygen as a tracer.

For example, when amyl acetate is hydrolyzed with water containing oxygen of weight 18, we find that the heavy oxygen does not enter the alcohol molecule; all of it is found in the acetic acid product:



For further discussion, see references 18 and 19, page 224.

Although the formula of an ester suggests that of a salt, there is a wide difference between the properties of these two groups. Thus many of the salts are water-soluble and they ionize quite readily, giving rapid reactions in water solution. The esters of low molecular weight are neutral liquids, they are only sparingly soluble in water and they do not ionize.

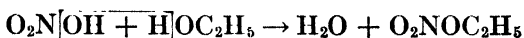
**Occurrence and Uses.** Esters of organic acids are natural products in the widest sense. Many of these compounds have pleasant fruity odors. They are found in fruits, flowers, and other parts of plants and are often responsible for the pleasant odors noted. Moreover, all of the natural fats and oils are mixtures of esters. Esters are made in large amounts to be used

\* The reaction of a halogen acid and an alcohol yields an alkyl halide, which type of compound would *apparently* belong with the esters because of its mode of formation. However, the reactions of the alkyl halides are entirely different from those of esters derived from carboxylic acids, in which the alkyl group is joined through oxygen to the rest of the molecule. Only those substances which are formed by loss of water between the hydroxyl groups of an acid and an alcohol should properly be classed as esters.

in perfumery, in medicines, and in the manufacture of artificial flavors, also as solvents for the preparation of lacquers (see page 635). Amyl acetate is in high favor as a solvent for pyroxylin lacquers (ethyl lactate and butyl and amyl esters are also used in this way). It is also used as an odor bait in grasshopper poison. Several of the formates are good fumigating agents. All esters have important synthetic applications, especially those which are related structurally to malonic ester and acetoacetic ester.

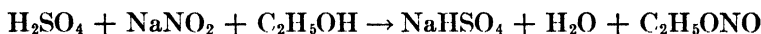
#### ESTERS OF INORGANIC ACIDS

Several esters of inorganic acids are important for their use in medicine, in industry, and in chemical synthesis. Among these is **Ethyl nitrate**,  $C_2H_5ONO_2$ , made by the action of nitric acid upon ethyl alcohol:



**Methyl nitrate**,  $CH_3ONO_2$ , is a powerful explosive but not of practical use.

**Ethyl nitrite**,  $C_2H_5ONO$ , is formed by the reaction of nitrous acid and ethyl alcohol:



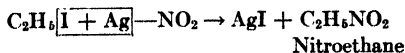
Ethyl nitrite, dissolved in alcohol, is sold as "sweet spirit of niter" for medicinal use.

**Amyl nitrite**,  $C_5H_{11}ONO$ , prepared in the same manner as shown for ethyl nitrite, is used in medicine in the treatment of asthma and epileptic convulsions, as an antispasmodic and in other ways. Alkyl nitrites hydrolyze in acid solutions with great rapidity, thus both amyl and ethyl nitrite are used in chemical operations as a source of nitrous acid.

**Triethyl phosphate**,  $(C_2H_5)_3PO_4$ , dissolves cellulose nitrate and cellulose acetate and may be used in making plastics and coating compositions. It is valuable for coating since it burns with great difficulty.

#### NITRO COMPOUNDS

It was shown on page 82 that the reaction of an alkyl halide with the salt of an acid yields the corresponding ester of the acid. When *silver* nitrite is employed in this manner to make ethyl nitrite, the ester is obtained as usual, but along with it varying amounts of the nitroparaffin are produced (V. Meyer, 1872).

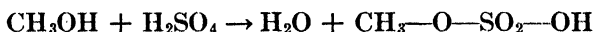


In a nitroparaffin, hydrogen of a saturated hydrocarbon has been replaced by nitro group,  $NO_2$ . The nitroparaffins are isomeric with the alkyl nitrites, but have different reactions because in them the nitrogen is directly attached to carbon, and not through the medium of oxygen. They are not subject to hydrolysis like esters, and yield amines on reduction (page 305).

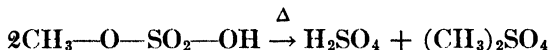
Up to recent years aliphatic nitro compounds had only an academic interest. With the discovery of a new method of preparation several members have become available for study and have aroused much interest. See Chapter XV for further discussion.

**Methyl sulfate**,  $(\text{CH}_3)_2\text{SO}_4$ , is made as follows:

(1) Reaction of methyl alcohol and sulfuric acid yields methyl hydrogen sulfate:



(2) The distillation of methyl hydrogen sulfate under diminished pressure produces methyl sulfate:

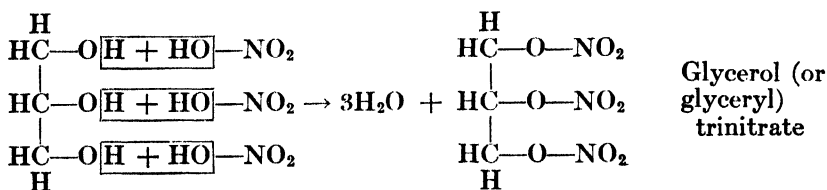


Methyl sulfate can be made very cheaply and is much used in synthetic work as a "methylating agent" (to introduce the methyl group into compounds). It is extremely poisonous and should be handled with caution; good ventilation is essential.

**Ethyl hydrogen sulfate**, or ethylsulfuric acid,  $\text{C}_2\text{H}_5\text{OSO}_3\text{H}$ , formed from ethyl alcohol and an excess of sulfuric acid, or from ethylene and sulfuric acid, has already received mention (pages 53 and 123). Heated alone this compound yields ethylene, while with alcohol ether is formed.

**Ethyl sulfate**,  $(\text{C}_2\text{H}_5)_2\text{SO}_4$ , has synthetic uses similar to those given for methyl sulfate. It is not as toxic as the methyl ester.

**Glycerol trinitrate**, (nitroglycerin), is prepared commercially by adding glycerol slowly to a mixture of concentrated sulfuric and nitric acids, meantime keeping the temperature below  $20^\circ$ .



The product of the reaction when purified is a colorless, heavy liquid of oily consistency, which has a sweet taste. Nitroglycerin finds somewhat the same medical use as does amyl nitrite; both cause dilatation of the arterioles, with a resulting fall of blood pressure. It is principally used as an explosive. Nitroglycerin if unconfined will burn quietly, but if heated to about  $218^\circ$  or subjected to shock it explodes. Taken up by kieselguhr, a porous infusorial earth, or (in modern practice) by wood powder, it forms the product called *dynamite*, which because of the separation of the droplets of nitroglycerin in the pores of the wood, is considerably safer to handle than the unprotected liquid.

Nitroglycerin is used to shoot oil wells and open safes. Dynamite is much more familiar to the public in connection with farming (stump removal), road building, erection of dams and bridges, and other building operations requiring leveling and removal of rock and earth. Nitroglycerin has a relatively high melting point ( $13.3^\circ$ ) hence dynamite made with it

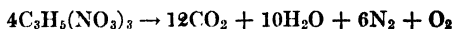
alone could freeze in winter, and attempts to thaw it would be dangerous. The melting point may be lowered by admixture of glycol dinitrate. By blending inorganic nitrates (sodium, ammonium) the complete burning of the wood powder is assured and a larger volume of gas is produced. Modern dynamites contain less nitroglycerin, more ammonium nitrate than those formerly made; hence they are safer.

**Explosives.** An explosive is valuable for its "brisant," that is, shattering, effect, if it is used like dynamite to break up rock, or for its "propellant" effect if it is to throw a missile from a gun. In the former case the explosion is rapid and the maximum pressure is very quickly attained; with propellants the maximum pressure is more slowly attained.

Requirements of an explosive vary somewhat according to the use for which it is intended, but for all types we are interested in a cheap starting material such as glycerol, and safety during manufacture and transportation. Many important explosives withstand ordinary shocks and jars quite well and must be fired by the use of detonators. These are substances such as mercury fulminate or lead azide which explode with extreme violence when struck.

A modern explosive is not a mixture like gunpowder. Here we have an oxidizing agent, potassium nitrate, and reducing agents, charcoal and sulfur, which even in the finest powder form are still quite far apart. The modern explosive has oxidizing and reducing groups as parts of the same chemical molecule. In nitroglycerin these are respectively the nitrogen atoms from the nitric acid and the carbon atoms from the glycerol. A modern explosive gives the maximum of gaseous products and leaves the minimum of inorganic residue. The latter point has especial value if the explosive is to be used in a gun.

The formal equation for the explosion of nitroglycerin is:



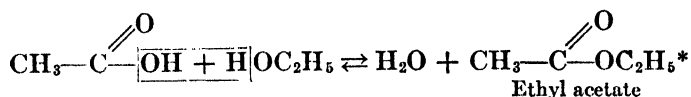
Some nitric and nitrous oxides are usually formed in the explosion.

The temperature reached is stated to be  $3470^\circ\text{C}$ . and the pressure of hot gases about 2000 atmospheres. The speed of the explosion wave through the nitroglycerin is about five miles per second.

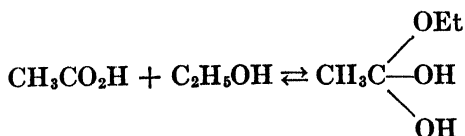
### ESTERS OF ORGANIC ACIDS

Esters of organic acids are prepared either from the acid or from the more reactive substances, acid anhydride or acid chloride, as follows:

(1) Formation of an ester from acid and alcohol:

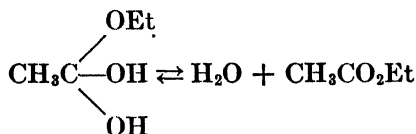


This is the formal or diagrammatic equation ordinarily used. It does not show the mechanism of the reaction. One theory states that in the first phase of reaction the alcohol adds to the carbonyl group of the acid:



\* It is customary to print the formulas of organic compounds with the characteristic group or most active part of the molecule, to the right hand.

and that in a second phase the intermediate compound loses water (typical reaction for a carbon bearing two hydroxyl groups):



This reaction is reversible; i.e., water acting upon ethyl acetate will yield ethyl alcohol and acetic acid. For this reason the equation is written with a double arrow, to show that it may be read either from left to right or vice versa with equal fidelity to the facts.

If equal molecular proportions of ethyl alcohol and acetic acid are taken for this reaction, equilibrium will be established when  $66\frac{2}{3}\%$  of each of these components has been converted to ester. Likewise, if equal molecular proportions of ester and water react, an equilibrium will result when  $33\frac{1}{3}\%$  of the ester has been changed to acid and alcohol. Both reactions, esterification and hydrolysis, are apt to be slow. If the alcohol and acid are merely left together at room temperature, many months elapse before equilibrium is attained. Formation may be catalyzed by the addition of a strong acid, such as sulfuric acid, or an aromatic sulfonic acid; nonacid materials, such as alumina or silica gel are also effective. The use of either acid or base will catalyze the hydrolysis. While the application of heat or a catalyst in either case will hasten the attainment of equilibrium, it will not alter the proportions given above, which obtain at equilibrium.

Acquaintance with the law of mass action, which governs reversible reactions such as the above, shows how we may increase the amount of ester produced in the process. We may (1) increase the "active mass" of one of the reacting products, that is use more alcohol or acid than is called for by the equation. The question of cost would determine which of these to add in excess, acid or alcohol. This procedure will increase the yield of ester, and also the cost of the process. The ester yield may also be improved by (2) removing one of the products of reaction, ester or water. If the ester has a low boiling point, it will suffice merely to distil it away from the mixture. However it is ordinarily quite satisfactory to remove the water, using concentrated sulfuric acid or other "water-remover."\* Sulfuric acid used in this role acts both as catalyst and water-remover and hence both speeds the reaction and improves the yield.

**Equilibrium Constant.** The figures given above may be used to obtain the constant for the esterification. It will be remembered that for the reversible reaction  $A + B \rightleftharpoons C + D$  we have the following expression:

\* The following list of substances used as "water-removers" in organic reactions and also as drying agents, may be helpful. Phosphorus pentoxide; sulfuric acid; zinc chloride; hydrogen chloride; sodium; calcium; potassium or sodium hydroxide; copper sulfate; oxalic acid; calcium oxide, carbide, or chloride; acetic anhydride; etc.

$$K = \frac{[C][D]}{[A][B]}$$

$K$  being the equilibrium constant and  $[C]$  representing the active mass, that is moles per liter concentration of  $C$ , etc. Hence for the esterification equilibrium we have:

$$K = \frac{[\text{Water}][\text{Ester}]}{[\text{Acid}][\text{Alcohol}]}$$

$$\text{or: } K = \frac{66.6 \times 66.6}{33.3 \times 33.3} = 4$$

We may use this figure to obtain the yield of ester for any mixture of acid and alcohol. Thus suppose 3 moles of acid and one mole of alcohol to have been used. Let  $x$  moles of ester be formed at equilibrium. Then  $x$  moles of water will also be present. The amount of alcohol left (in moles) will be  $1 - x$  and of acid there will be  $3 - x$ . Therefore we solve the equation:

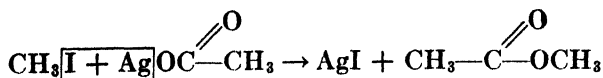
$$\frac{x \cdot x}{(3 - x)(1 - x)} = 4$$

to find  $x$ , which is the yield of ester in moles. A calculation of this kind shows that good yields of ester can be obtained only by the use of large relative concentrations of alcohol or acid; that is, it is far more practical to remove ester or water than to add alcohol or acid, and that the best possible results are obtained when an excess of alcohol or acid is used, coupled with removal of water or ester from the reaction field. In industrial practice this is the method used. As already stated, primary alcohols esterify most easily and tertiary with greatest difficulty. The yields of esters are therefore comparatively much greater for primary alcohols, and least for tertiary alcohols.

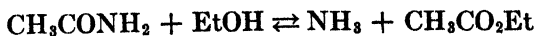
(2) Use of acid anhydride and alcohol; see equation on page 192. No water is produced in this reaction (a molecule of water is removed when an acid anhydride is made from an acid); hence it is not reversible like (1) and proceeds to completion.

(3) Ester formation from acid chloride and alcohol; equation on page 189. This reaction goes quickly to completion because the by-product, hydrogen chloride, is a gas which is able to leave the field of reaction.

(4) Esters may also be made by the use of an alkyl halide and the salt of an acid:



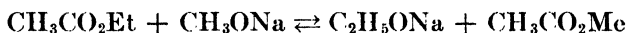
(5) Esters may be made by action of an alcohol on an amide:



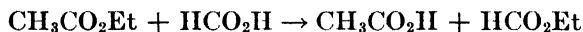


The reaction, which is reversible, is carried to completion by the use of an acid to take up the ammonia. Another method of going from amide to ester is given on page 229.

(6) An ester may be made from another ester by exchange of alkyl radicals; the reaction is known as *transesterification* or *cross esterification*.



As catalyst an acid or (better) an alkoxide is used. Exchange of a radical for one of higher weight as shown above is easier than the contrary. We may also exchange the acid radical of an ester as shown below ('acidolysis'):

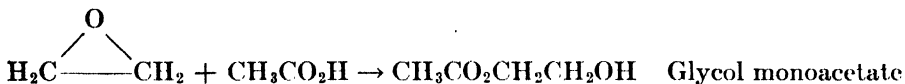


(7) The formation of an ester by direct addition is exemplified by the reaction of olefins with sulfuric acid (page 56). In ketene,  $\text{CH}_2=\text{C}=\text{O}$ , we have a highly reactive unsaturate which can form acetates by addition.

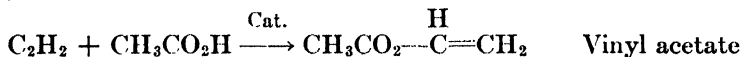
Example:



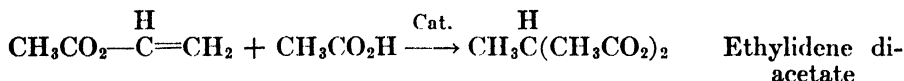
Ethylene oxide functions in somewhat the same way, i.e., it can perform an addition upon rupture of the oxygen bridge:



A further example of esterification by addition is the formation of vinyl esters from acetylene treated with an acid in the presence of mercury sulfate:



A second addition yields:



The second reaction is retarded by using an excess of acetylene. Vinyl esters polymerize easily, are important for the making of Vinylite resins (see page 506). Ethylidene diacetate is used to make acetic anhydride (see page 191).

(8) Esters may be made from nitriles, from aldehydes, from certain of the olefins. An interesting synthesis is that from aldehydes. It will be remembered that formaldehyde with strong base gives formic acid and methanol (self-oxidation and reduction). Acetaldehyde does the same when treated with aluminum ethoxide. Thus:



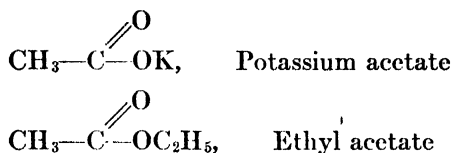
The acid and alcohol esterify at once under the conditions imposed. This is called the Tishchenko reaction. The yield of ethyl acetate is about 95% (see page 149).

The large number of methods used for the production of esters is quite justified by the extreme importance of these compounds for synthesis, for various industrial purposes, and in daily life.

#### NOMENCLATURE OF ESTERS

Esters are named like salts when they are made from monohydroxy alcohols.

Examples:

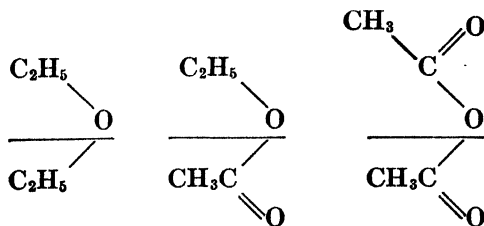


Esters made from a polyhydroxy alcohol have names beginning with the alcohol name and ending with the names of the acid groups introduced; example, glycerol trinitrate, page 200.

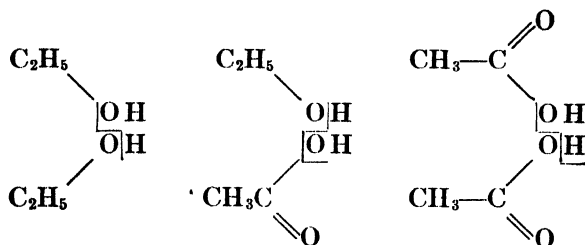
#### REACTIONS OF ESTERS

(1) *Hydrolysis*. Esters heated with water break down to yield the corresponding acid and alcohol. (A basic or acidic solution will accomplish this sooner.) Such hydrolysis when carried out in a basic solution so as to produce an alcohol and a salt is called *saponification*; the name arises from the fact that the hydrolysis of a fat (fats are esters) with strong base yields a soap. (See page 218.)

It should be noted that the esters, the acid anhydrides, and the ethers are compounds with somewhat similar structure:



They are formed by the same type of reaction, loss of water between hydroxyl groups:



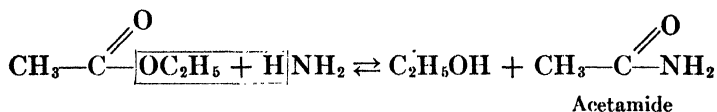
All are subject to hydrolysis, but not with equal facility. In reactivity the esters lie between the ethers and the anhydrides.

This is reasonable if we take into account the structures of the compounds. In a hydrocarbon or an ether we have a fairly symmetrical distribution of electrons and consequent strong bonding between C—C and C—O, but in the ester and acid anhydride the presence of carbonyl upsets the symmetry. (The same is true of acid chlorides which hydrolyze well.) It is likely that the first step of the hydrolysis involves the addition of water to the carbonyl group; this is followed by the breaking of the C—O bond.

The presence of hydrogen ion increases the speed of hydrolysis of an ester, the rate being proportional to the hydrogen ion concentration. This gives a reliable method of comparing the strengths of acids (by using them to hydrolyze a given ester and noting the relative speeds of hydrolysis).

When a base is used the hydrolysis is not only much more rapid than with an acid but the reaction product (organic acid) is neutralized by the base, forming a salt; hence the reaction cannot reverse.

(2) *Reaction with ammonia:*



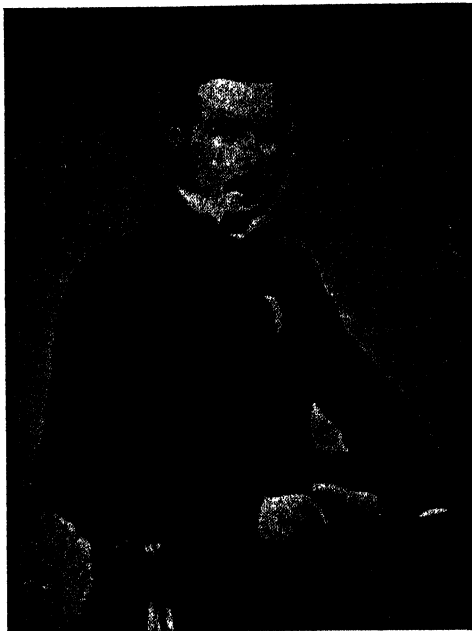
The corresponding amide is formed by this reaction, and the alcohol of the ester is set free. This reaction is reversible but at equilibrium the concentration of ester is very low and the yield of amide practically quantitative.

(3) *Reduction.* It will be remembered that direct reduction of acids is not practical. The reduction of an ester is, however, a valuable means for effecting reduction of the carboxyl group. The products are two alcohols, one of which corresponds to the acid from which the ester was made:

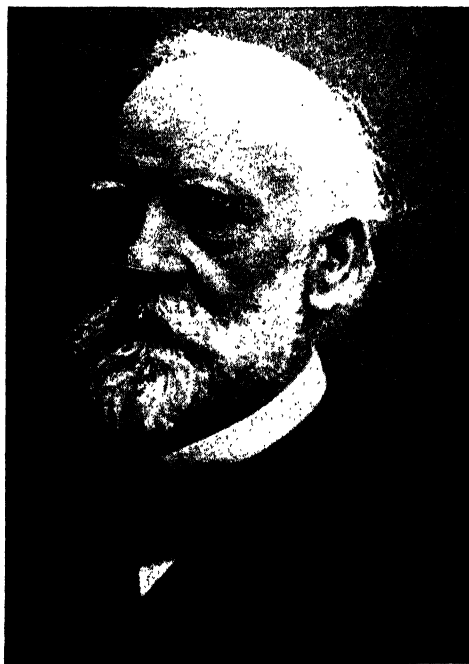


The reduction may be accomplished by the use of sodium and alcohol; commercial practice is to employ catalytic hydrogenation, using hydrogen with copper chromite. The reaction temperature is 200°+. the pressure

**ARCHIBALD S. COUPER.** (1831-1892, Scotch.) Couper deserves credit equal to Kekulé's for proposing structural formulas for organic compounds. His paper was accidentally delayed until that of Kekulé had been published. See *J. Soc. Chem. Ind.*, **50**, 931 (1931), *J. Chem. Education*, **7**, 2808 (1930), *ibid.*, **11**, 331 (1934).



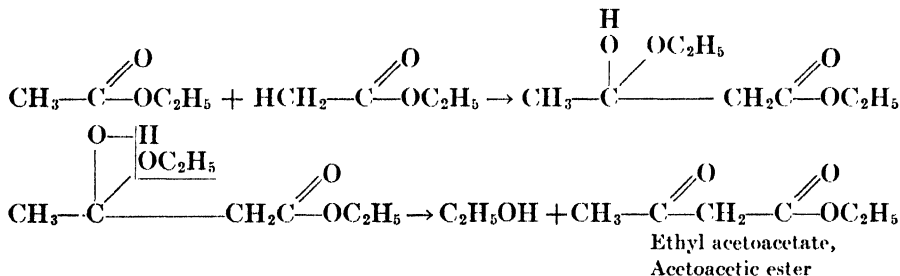
*Journal of Chemical Education*



**CHARLES FRIEDEL.** (1832-1899, French.) Friedel was interested in both mineralogy and chemistry. He studied chemistry in Wurtz's laboratory; here he worked on aldehydes and ketones and discovered isopropyl alcohol. Later he became professor of organic chemistry at the Sorbonne, succeeding Wurtz. Friedel did much work with organic compounds of silicon; he performed the synthesis of glycerol from acetone. He is best known in connection with the Friedel-Crafts reaction. See *J. Chem. Soc. (London)*, **77**, 993 (1900); Thomas, *Anhydrous Aluminum Chloride in Organic Chemistry*, Reinhold Pub. Corp., 1941; also this book, page 575.

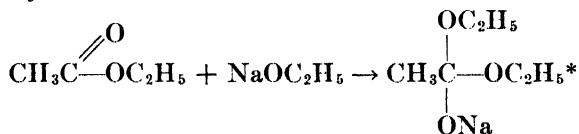
about 3000 pounds per square inch. The method is applied to esters of the higher acids, including the glycerides. The long-chain alcohols are valuable for use in perfumes, for aldehyde manufacture, and for the preparation of new type detergents (page 220).

(4) *Claisen condensation*. In the presence of metallic sodium and a trace of alcohol, certain esters undergo condensation with themselves, or other compounds. Thus ethyl acetate condenses with itself to yield the important compound ethyl acetoacetate (acetoacetic ester), as shown schematically in the following equation:

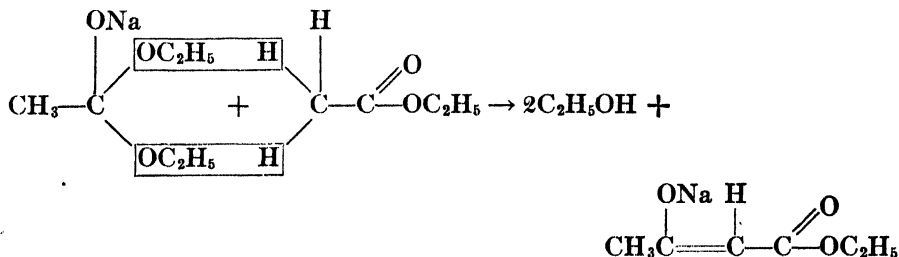


The condensation of ethyl acetate to acetoacetic ester is believed to take place in several steps. Following is Claisen's theory of the reaction.

(a) The sodium reacts with the small amount of ethyl alcohol present to form hydrogen and sodium ethoxide, the latter then uniting with a molecule of ethyl acetate:



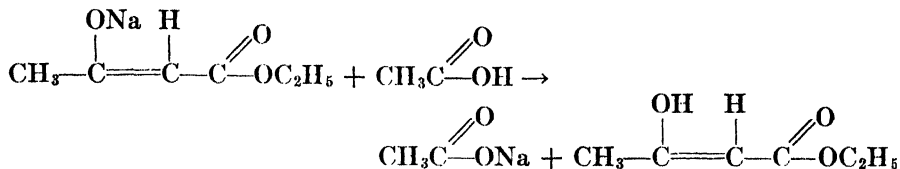
(b) The addition-product next reacts with another molecule of ethyl acetate to form the sodium salt of acetoacetic ester and ethyl alcohol.



The ethyl alcohol so released is again converted to sodium ethoxide, which is able to convert further quantities of ethyl acetate to acetoacetic ester.

\* This addition compound has not been isolated. The sodium ethoxide seems to be a catalyst but perhaps does not react in the manner shown here. The most recent theory regarding the Claisen condensation will be found in references 47, 48, page 225.

(c) Treatment of the sodium salt of acetoacetic ester with an acid yields the free ester:

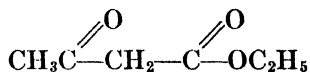


The reaction in its simplified form as shown on page 208 should be compared with that for the formation of aldol (page 148) which it closely resembles. The **commercial method of preparation** is given on page 292.

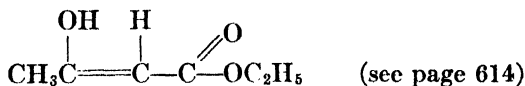
Acetoacetic ester lends itself to the preparation of a number of different substances, being extremely versatile in synthetic applications. It will be profitable to review the behavior of this compound in some detail.

#### ACETOACETIC ESTER

Acetoacetic ester has in the past aroused considerable interest among chemists, because of the conflicting nature of its reactions, which are at the same time those of a ketone, and of an unsaturated alcohol. No one formula could be assigned to the compound which would justify these different reactions. The explanation of this seeming conflict lies in the fact that the substance is tautomeric, and exists at one and the same time in two forms, one, termed the *keto* form, having the following structure:



while the other, called the *enol* type, is:



We have noted this same behavior in the case of acetaldehyde (page 145). In the case of acetoacetic ester, both forms of the compound have actually been isolated, and the change of one type to the other under various conditions has been studied.

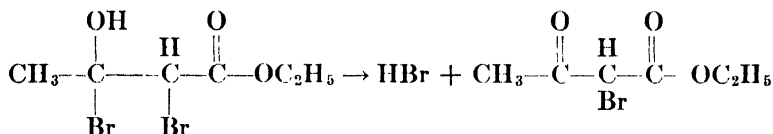
A sample of the ester at ordinary temperature contains both keto and enol forms in equilibrium with each other; about 8% is enol and the balance is in keto form. Any reagent which removes one form of the ester by reacting with it will cause more of this form to appear by intramolecular rearrangement; that is, a tautomeric change of this sort obeys the law of mass action for reversible reactions. For example, if a certain reagent reacts with the keto form, more and more of this tautomer will be formed from the enol tautomer to take the place of the molecules which have been removed; the entire sample will react as a ketone.

The change from one form to the other involves the shifting of a hydrogen atom, as in most other forms of tautomerism. When, as in this case, both tautomers may be isolated, they are called *desmotropes*, and the phenomenon is known by the name of *desmotropy*.\*

#### REACTIONS OF ACETOACETIC ESTER

The *keto tautomer* of acetoacetic ester adds hydrogen cyanide and it forms both an oxime and a bisulfite compound, reactions typical of the ketone structure.

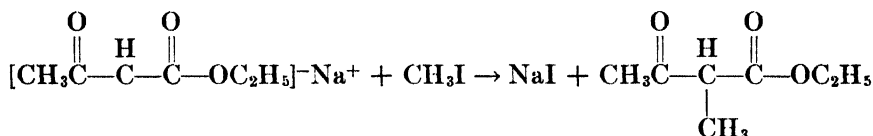
The *enol form* shows its *unsaturation* by its reaction with bromine, which is added and apparently forms a dibromo compound that loses hydrogen bromide very easily:



Acetoacetic ester, treated with ferric chloride, gives a deep color; the same behavior is shown by other compounds known to have *hydroxyl group*.

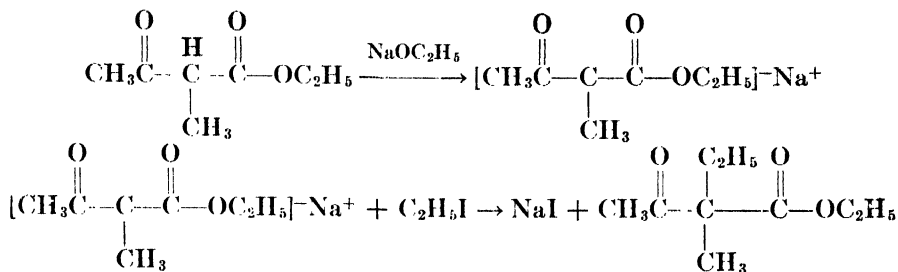
The presence of a hydroxyl group is also shown in the fact that the ester forms a sodium salt. The ester dissolves in dilute alkali but is not sufficiently acidic to dissolve in sodium carbonate solution. The ionization constant is about  $1 \times 10^{-12}$ . The sodium salt is a derivative of the enol form of the ester, but it is not feasible to assign it a graphic formula, because, as will be shown later, the enol contains a hydrogen bridge (see page 127). A structural formula which leaves the position of sodium undetermined will be used instead.

**Alkylation of the Ester.** In the various syntheses with acetoacetic ester, the sodium salt is usually the starting compound. It may, for instance, be treated with an alkyl halide. By such a reaction the alkyl group is substituted for hydrogen atom of the methylene group of the ester.

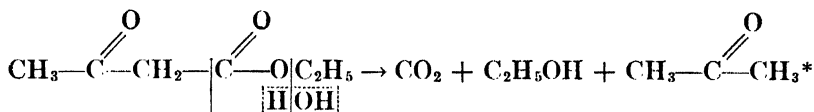


The second hydrogen of the  $\text{CH}_2$  group may now be replaced by sodium and another alkyl group introduced as before:

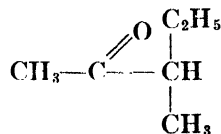
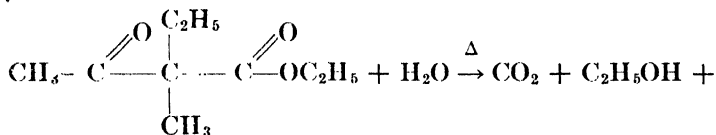
\* This term, formerly often used, is apparently being dropped. The general phenomenon of tautomerism (ionotropy) covers both prototropy (migration of proton) and anionotropy (migration of an anion). Though the prototropic change has been figured in this book as involving a shift of hydrogen, the actual steps are probably (1) loss of a proton, leaving a negative ion, (2) electronic shifts in the negative ion which place the free electron pair in a new position, (3) addition of a proton in the new position.



**Hydrolysis of the Ester.** Two distinct classes of substances are produced by the hydrolysis of acetoacetic ester or its alkyl substitution products. If the hydrolysis is accomplished by dilute alkali or acid, ketones are formed (ketone hydrolysis):

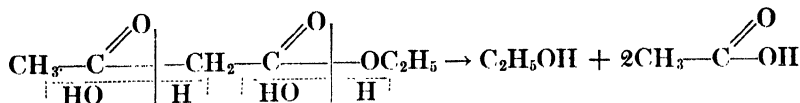


By the hydrolysis of a substance like that shown above, in which alkyl groups have been introduced, we obtain an alkyl-substituted ketone:



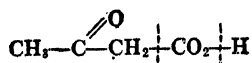
Methyl *sec* butyl ketone

The hydrolysis of acetoacetic ester by a concentrated alkali yields acids (acid hydrolysis):

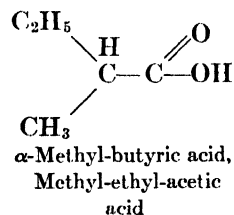
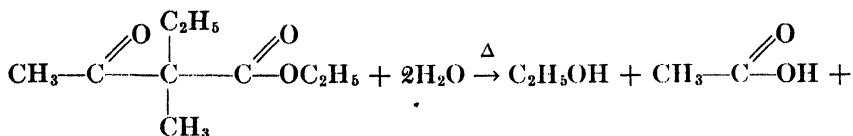


Therefore the substituted ester just discussed would be capable, by this type of hydrolysis, of producing a dialkyl-substituted acetic acid:

\* The acetone and carbon dioxide result from the decomposition of acetoacetic acid:







The two types of hydrolysis shown here take place side by side. By choice of the proper conditions one is able to favor the desired reaction, but it is impossible to completely suppress one reaction in favor of the other.

It is easily seen that these reactions of substitution and hydrolysis allow the formation of many derivatives of both ketones and acids.\* Only the simplest applications have been discussed here; other uses of the ester, of which there are many, are more suitable for advanced study. The reaction of acetoacetic ester with phenylhydrazine by which antipyrine is prepared is shown on page 486. For the use of acetoacetanilide, a valuable dye intermediate, see page 681.

#### PHYSICAL PROPERTIES OF ESTERS OF ORGANIC ACIDS

Esters, except those of high molecular weight, are liquids. They are neutral substances, colorless, usually of pleasant odor. In general they are lighter than water. The lower esters are somewhat water-soluble; solu-

TABLE 18.—BOILING POINTS OF ESTERS

Acid radical	Methyl	Ethyl	n-Propyl	n-Butyl	n-Amyl
Formic.....	32	54.0	81.3	106.9	130.4
Acetic.....	59-60	77.1	101.6	125.1 (740)	148.4 (737)
n-Propionic.....	79.7	99.1	122-3	146	160.2 (iso)
n-Butyric.....	102.3	121.3	142.7	165.7 (736)	178.6 (iso)
n-Valeric.....	127.3	145.5	167.5	168.7*	194†
Nitrous.....	— 12	17	57	67-8 (iso)	104
Nitric.....	65	87-8	110.5	122.9 (iso)	147-8 (iso)

\* Isobutyl isovalerate.

† Isoamyl isovalerate.

\* The reaction is not well suited to the preparation of di-substituted ketones; the preparation of acids is often more conveniently carried out by means of the malonic ester synthesis (page 257).

bility decreases with rise of molecular weight. Esters are freely soluble in alcohol and ether.

Inspection of the table on p. 212 shows that esters have low boiling points, often lower than those of the acids and alcohols involved in their preparation. The structure of an ester is such that it cannot associate as can either acid or alcohol; hence it has a "normal" boiling point (see page 126).

#### DETECTION AND IDENTIFICATION OF ESTERS

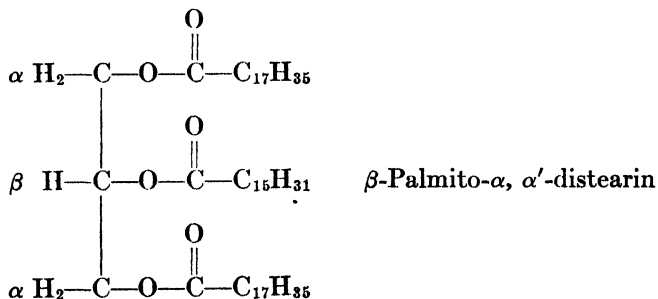
The presence of an ester is suspected when the compound in hand has the physical properties enumerated above and the characteristic ester odor. Esters are soluble in cold concentrated sulfuric acid, and those with fewer than nine carbon atoms dissolve in phosphoric acid.

An ester is identified by first saponifying it, then making separate identification of the acid and alcohol produced in the saponification.

#### FATS. OILS

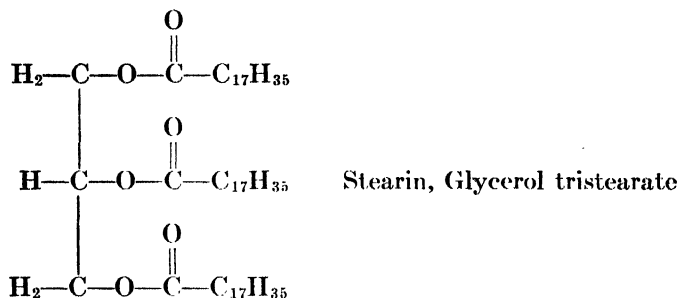
The fats and fixed oils are esters of a special class, inasmuch as all are derived from glycerol. They deserve a separate mention for this reason, and also because of their great importance as foods, and their extensive use in industry and medicine. Ordinarily by the term fat one refers to a substance which is solid at room temperature, liquids being termed oils.\* The low melting points of the oils are frequently due to the higher percentage of unsaturated radicals in their molecules as compared with the molecules of the fats.

The formula for a typical fat ester is:



These substances are known as triglycerides. The name of any one of them is based upon the names and positions of the acids which are esterified with glycerol. Such names frequently end in "in." The substance shown above is a mixed glyceride. Stearin, or tristearin, shown below is a simple triglyceride.

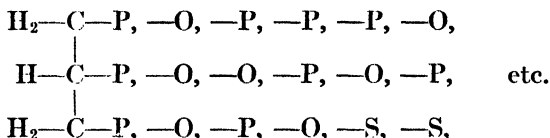
\* One should distinguish sharply between the oils considered here, fixed oils or fatty oils, the mineral oils (Chapter II), and the essential oils (Chapter XXXIII).



**Preparation.** Fats and oils are obtained from vegetable tissues (seeds, fruits) by breaking the tissues and applying pressure. Solvent extraction is also used. Some fats can be rendered. The crude animal matter is heated in water, whereupon the fat melts and floats on the water. Purification of fats and oils is effected by straining, or filtration.

**Physical Properties.** Fats are colorless, odorless, and tasteless. They have a specific gravity less than that of water. Insoluble in water, they are but sparingly soluble in alcohol, and freely soluble in carbon disulfide, turpentine, carbon tetrachloride, ether, light petroleum oils, etc. Fats themselves are good solvents; thus in perfume making, lard has been used to extract the flower oils from the flower petals. Fats may not be distilled at ordinary pressure without decomposition.

**Structure.** A fat molecule may be a mono-, di-, or tri-glyceride; if a di- or triglyceride, it may be either simple or mixed. In nature mixed triglycerides are the rule. Both saturated and unsaturated acids (with double bonds) are found in their molecules. When several different acids are combined with glycerol, different compounds result, as shown herewith. In this case the acid radicals are shown as P, O, and S.



If ten different monocarboxylic acids are combined in all possible ways, 550 different triglycerides may be produced.

**Acids Used in Fats.** The acids found in fats are straight-chain saturated monocarboxylic acids with from 4 to 30 carbon atoms, and unsaturated straight-chain acids, monocarboxylic, with from 4 carbons up. The acids found in fats have an even number of carbons. The most important ones are oleic, palmitic, stearic, linoleic, and linolenic acids.

**Chemical Properties of the Acids.** The physical and chemical properties of the saturated acids were taken up in Chapter VIII. For the higher acids found in fats the most important derivatives are the salts (soaps) and the esters. The unsaturated acids may be reduced to saturated acids of

TABLE 19.—COMMON ACIDS OF FATS

Name	Formula	M.p.	Source
Butyric.....	$C_4H_8O_2$	— 4 7	Butter fat
Caproic.....	$C_6H_{12}O_2$	— 1.5	Butter fat, coconut oil
Caprylic.....	$C_8H_{16}O_2$	16.0	Coconut oil, palm oil, butter
Capric.....	$C_{10}H_{20}O_2$	31.5	Butter fat, coconut oil
Lauric.....	$C_{12}H_{24}O_2$	47-8	Coconut oil, spermaceti
Myristic.....	$C_{14}H_{28}O_2$	57-8	Nutmeg oil, butter fat
Palmitic.....	$C_{16}H_{32}O_2$	63-4	Palm oil, animal fats
Stearic.....	$C_{18}H_{36}O_2$	69 70	Beef, mutton tallow
Arachidic.....	$C_{20}H_{40}O_2$	77	Arachis oil (peanut)
Behenic.....	$C_{22}H_{44}O_2$	84	Beet oil
<i>One double bond</i>			
Oleic.....	$C_{18}H_{34}O_2$	14	Almond lard oil, peanut oil
Erucic.....	$C_{22}H_{42}O_2$	33-4	Rape oil, mustard oil
<i>Two double bonds</i>			
Linoleic.....	$C_{18}H_{32}O_2$	< -18	Cottonseed oil, peanut oil
<i>Three double bonds</i>			
Linolenic.....	$C_{18}H_{30}O_2$	.....	Linseed oil
<i>Four multiple bonds</i>			
Clupanodonic.....	$C_{22}H_{34}O_2$	< -78	Fish oils, whale oil

corresponding structure. This is done with hydrogen in presence of a catalyst.

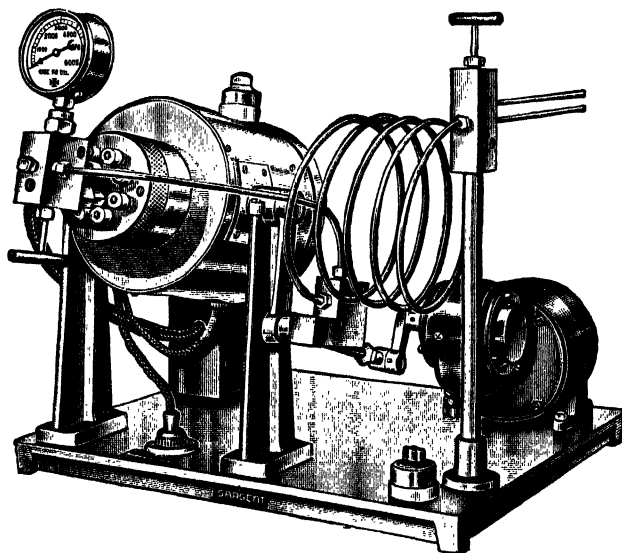
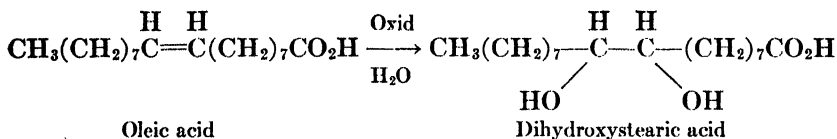
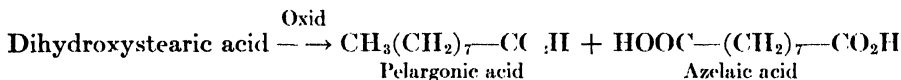


FIG. 31.—Apparatus for catalytic hydrogenation at high pressure and temperature. (Sargent and Company.)

The mild oxidation of an unsaturated acid yields a dihydroxy acid (see reactions of ethylene):



More powerful oxidation splits the molecule at the site of the double bond giving two acids, one of which is, of course, dicarboxylic. The location of the double bond is determined by examination of the products. The reaction with ozone may be used for the same purpose (see p. 57).



As would be expected, the unsaturated acids add bromine and iodine readily at the double bonds.

TABLE 20.—ACID CONTENT OF FATS AND OILS

Name	Oleic	Lino- leic	Lino- lenic	Stearic	Myristic	Palmitic	Arachidic
Butter*	27.4	....	....	11.4	22.6	22.6	
Mutton tallow	36.0	4.3	....	30.5	4.6	24.6	
Castor oil†	9	3	....	3			
Olive oil	84.4	4.6	....	2.3	trace	6.9	0.1
Palm oil	38.4	10.7	....	4.2	1.1	41.1	
Coconut oil‡	5.0	1.0	....	3.0	18.5	7.5	
Peanut oil§	60.6	21.6	....	4.9	....	6.3	3.3
Corn oil	43.4	39.1	....	3.3	....	7.3	0.4
Cottonseed oil	33.2	39.4	....	1.9	0.3	19.1	0.6
Linseed oil	5	48.5	34.1				
Soybean oil¶	32.0	49.3	2.2	4.2	....	6.5	0.7
Tung oil**	14.9	....	....	1.3	....	4.1	

\* Contains caproic, 1.4%; caprylic, 1.8%; capric, 1.8%; butyric, 3.2%; lauric, 6.9%.

† Contains about 85% of ricinoleic acid, 12-hydroxy-9-octadecenoic acid (m.p., 17°),  $\text{CH}_3(\text{CH}_2)_8\text{CHOHCH}_2\text{CH}=\text{CH}(\text{CH}_2)_7\text{COOH}$ .

‡ Contains caprylic, 9.5%; capric, 4.5%; lauric, 51%.

§ Contains 2.6% lignoceric acid.

|| Contains 0.2% lignoceric acid.

¶ Contains 0.1% lignoceric acid.

\*\* Contains 79.7% eleostearic acid.

**Chemistry of the Fats.** First in importance is the reaction of hydrolysis, which may be carried out with superheated steam alone, or with the help of acid or base. The latter process, which yields soaps, is called saponification. Certain enzymes (lipases) which occur in nature also promote hydrolysis of fats.

*Rancidity of fats* may be due to hydrolysis upon standing, which in the case of butter yields volatile acids of unpleasant odor. Another form of

rancidity is due to oxidation of unsaturated fats promoted by light and heat. This oxidation yields aldehydes and acids which have strong odors.

*Hydrogenation of oils* is practised in order to raise the melting point of oils for use in the kitchen, for soap making, and for the preparation of margarin. There is a prejudice against the use of oil in cooking in this country with a preference for the use of lard. By heating a vegetable oil with hydrogen under pressure in the presence of finely divided nickel, it is possible to reduce and hydrogenate the double bonds of the acid chains *in situ*\* to such a point that the material on cooling will be a semi-solid, similar to lard. Crisco, Snowdrift, Spry, are made in this way from vegetable oils. Complete hydrogenation would give a hard and brittle solid unsuitable for the purpose intended.

A butter substitute (Olcomargarin) may be made by mixing hydrogenated oil with suitable vegetable fats, churning the mixture with milk or cream, adding salt, and perhaps a small amount of butter.

*Auto-oxidation of unsaturated oils* occurs in the case of some on exposure to light and moist air. Apparently oxygen is added at the double bonds, and possibly there is some polymerization. A tough, hard solid results after some time. Such oils are known as drying oils (linseed oil, hempseed oil, poppyseed oil, tung oil). They are used in paints and varnishes. The drying action may be hastened by the use of catalysts. "Boiled linseed oil," for example, has been heated with lead oxide in order to hasten its rate of hardening. Lead, manganese, and cobalt soaps are used in paints to hasten drying. Linoleum is a mixture of powdered cork and pigments, which is mixed with linseed or tung oil and spread on a cloth backing to harden.

**Analytical.** The highly complex nature of the natural fat mixtures makes necessary a number of physical and chemical tests in order to gain approximate ideas about their composition. Physical constants which have value are melting point, absorption spectrum, index of refraction, specific gravity, and viscosity.

*The total fat* in a commercial crude is obtained by extraction with hot ether in a special apparatus. The dried sample, placed in an extraction thimble, is continuously extracted with a small amount of ether. When extraction is complete, evaporation of the ether leaves the fat, which is weighed by difference. The Babcock test is used for fat in milk or cream. This is treated with concentrated sulfuric acid, which, reacting with the water present, liberates enough heat to melt and separate the fat. The fat layer rises to the top of the special bottle used, where a series of calibrated graduations allows one to measure the percentage of fat.

*The saponification number* is the number of milligrams of KOH needed to saponify one gram of fat. Saponification is accomplished by the use of standard alcoholic potash with a weighed sample of fat.

*Unsaponified Portion.* Any material in a sample which is not saponified by alkali may be extracted by the use of ether. The glycerol and soaps formed by the saponification remain dissolved in the water layer. Evaporation of the ether layer then gives a residue of unsaponifiable material (sterols, waxes).

*Reichert-Meissl Number.* This is the number of cc. of N/10 alkali required to neutralize the water-soluble volatile fatty acids resulting from the hydrolysis of five grams of fat. The

\* That is, without decomposition of the ester molecules of the oil.

fat is saponified by the use of a solution of sodium hydroxide in glycerol, after which the mixture is acidified with dilute sulfuric acid and distilled in steam. It will be remembered that the acids with carbon content up to 10 are volatile in steam. The distillate is chilled and filtered, and the titration of the filtrate gives the R/M number. From the titer of insoluble volatile acids we get the Polenske number. Butter has R/M number of 17-33 while that of cottonseed oil is less than 1.

The *iodine number* of a fat is a measure of unsaturation. It is the number of grams of iodine added by 100 g. of the fat. The sample, dissolved in a suitable solvent, is treated with an excess of iodine solution; after having stood a sufficient time, the amount of iodine which remains unreacted is determined by the use of sodium thiosulfate solution. Non-drying oils have an iodine number less than 100; a value more than 130 indicates a drying oil.

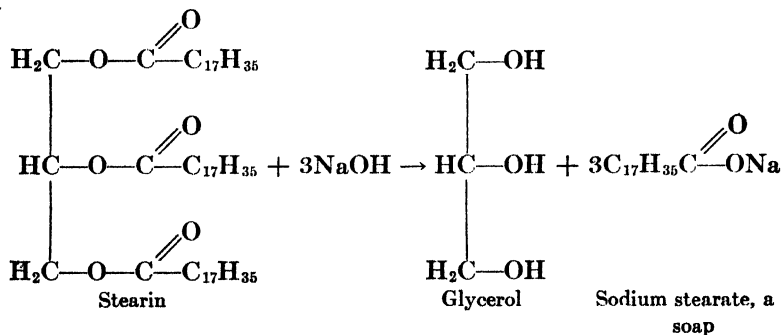
### SOAPS

Soluble soaps are by definition the sodium and potassium salts of saturated fatty acids having from eight to about eighteen carbon atoms. Those with sodium ion are hard soaps, and those with potassium are soft soaps, more water-soluble than the former. Soaps of other metals (aluminum, copper, lead, mercury, zinc) have special uses, but are not suitable for washing purposes.

Sodium and potassium salts, while water-soluble to a certain extent, are insoluble in fat solvents such as ether, petroleum oils, benzene, carbon tetrachloride, etc.

For hard soaps, oils and fats with a high percentage of saturated acids are desirable (beef and mutton tallow, palm oil, coconut oil, lard, hydrogenated vegetable or whale oils). Unsaturated acids, such as linolenic or elupano-donic, in a hard soap oxidize on standing and impart an unpleasant odor. Soft soaps employ linseed oil, cottonseed oil, and fish oils.

**Soap Making.** The most common method for the production of hard soaps involves the saponification of fats by alkali:



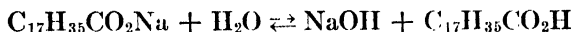
The fat is heated by live steam, and lye is added to start the saponification. After a time, sodium chloride is added to salt out and separate a portion of the soap, after which more lye is added and later more salt. The soap floats as an upper layer over a layer of spent lye, salt, and glycerol solution, which is drawn off and processed to obtain pure glycerol. The soap is again

treated with hot water and additional base, to complete the saponification, then after a period of standing is kneaded in the "crutcher" to insure a uniform composition. Fillers, perfumes, etc. are incorporated at this time. After standing in frames for some days to harden, the soap is cut into slabs and bars. The bars may be dried slowly, and then pressed into the final cakes, or the bars may be chipped and dried quickly. The chips are then milled and made into cakes.

Fats may be hydrolyzed by the use of live steam alone. The process would be very slow on account of the poor contact between fat and water, but is hastened by causing emulsification to take place by the addition of about one per cent of the Twitchell reagent (an aromatic sulfonic acid). The glycerol produced by this method is of course less contaminated to begin with than in the lye method. The fatty acids resulting from the hydrolysis are neutralized by the use of sodium carbonate. A portion of the stearic acid may be diverted for candle manufacture.

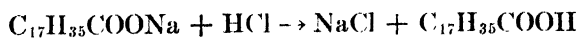
Substances added to soap include rosin soaps or sodium carbonate (to increase lathering power), various cleaners such as borax, sodium silicate, and fillers (clays, fullers earth, flour, bran, sawdust, sugar, moss). Perfumes may be added, or medicinal agents (camphor, phenol, thymol, sulfur, zinc oxide), or special solvents (benzene, decalin, carbon tetrachloride, tetralin). Inorganic salts or dyes are added to give color and mottled effects.

**Chemistry of Soap.** Soaps being salts of weak acids with a strong base, are somewhat hydrolyzed in water:

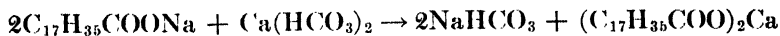


Soap exists in colloidal form in water solution and most of the fatty acid is adsorbed by the colloid, not free in the solution. Soaps may be precipitated ("salted out") from an aqueous solution by the addition of sodium chloride, as they are insoluble in brine.

By the action of a mineral acid, the free fatty acids may be secured from a soap (salt). These acids are practically insoluble in water, but freely soluble in ether, while the opposite holds true for the soap.



Sodium and potassium salts, as stated, are water-soluble, while the salts of calcium, barium, magnesium, copper, etc. are quite insoluble. Hard water thus gives a precipitate of the calcium (and magnesium) salts when soap is used with it:



Water may be softened in this way, though it is not an economical process. The hardness of water may be ascertained by a method based upon this reaction.

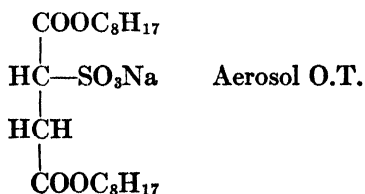


**Uses.** Soaps are useful for other purposes than cleaning. Several soaps are used to hasten the drying of paints (manganese, cobalt soaps). Copper and mercury soaps are used as disinfectants. The zinc salt of stearic acid is a component of many toilet powders. Lead plaster, or lead soap, is used in medicine. Stearates have many uses. Aluminum stearate is used in compounding greases for lubrication; aluminum, calcium, and other stearates are used as lubricants, for paper sizing, as antioxidants, in crayons, as waterproofing compounds, and in other ways. Soap is a good disinfectant. Most ordinary germs are killed by soapsuds. Soaps are also good insecticides.

**Cleaning Action of Soap.** When soap is dissolved in water, there is a large drop in surface tension. Thus water at 25°C. has a surface tension of 72 dynes per cm., while a 0.05% solution of a good laundry soap has a surface tension of about 30 dynes per cm. This lowering of surface tension facilitates the emulsification of grease and fat, and it also allows a better penetration of the soap solution into cracks and crannies.

The soap molecule has a long hydrocarbon chain and a polar carboxyl group. The hydrocarbon part has fat-dissolving properties, while the carboxyl group is attracted and held by water. Thus the emulsified fat is taken up by the soap molecules. A small droplet of fat can be pictured as surrounded by soap molecules, the alkyl chains of which would "point inward" being dissolved in the fat, while the carboxyl groups would "point outward" and repel other similar aggregates. The result would be a stable emulsion of fat in water. This treatment of detergent action of soap has ignored certain important points, and is not offered as a complete explanation of this phenomenon.

Detergents, emulsifying agents, and wetting agents are all classed as "surface-active" agents. Due to the polar nature of the molecules, discussed above, they have the ability to collect at a liquid-liquid or liquid-solid interface. Molecular weights of suitable compounds run from about 200 to 1000. Detergents are generally long-chain compounds with a water-soluble group at one end; wetting agents have the water-soluble group near the center of the molecule. An example is aerosol O.T.



**New Detergents.** One of the recent developments in the field of detergents is the preparation of sulfuric acid esters of higher alcohols (ten carbons up). The sodium salts of these esters are good detergents. They may be used in hard water or salt water, or in slightly acid solutions, where ordinary soaps fail. The general formula for these soaps is  $\text{RCH}_2\text{OSO}_3\text{Na}$ . An

example is  $\text{CH}_3(\text{CH}_2)_{10}\text{CH}_2\text{OSO}_3\text{Na}$ , sodium lauryl sulfate. The long-chain alcohols (lauryl, myristyl, palmityl, stearyl) are obtained by the catalytic reduction of fats, then treated with sulfuric acid, subsequently with alkali.

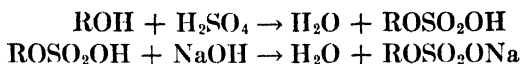
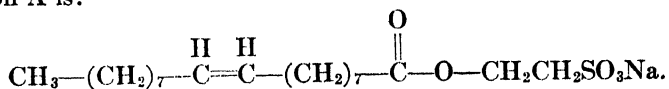


FIG. 32.—Model of a surface-active molecule. This is a polyoxyethylene derivative of a sorbitan monolaurate. (Courtesy of Atlas Powder Company.)

Trade names of several such products are Gardinol, Dreft, Orvus. The Igepons form another class of compounds with special advantages as detergents. They have several type formulas.

Igepon A is:



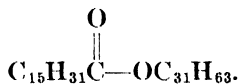
While there is no likelihood that these new detergents will displace soap for general purposes, they will without doubt do so in those special situations named above in which soap has been unsatisfactory. Some idea of the number of special wetting agents and detergents now available may be had from Reference 35, page 224. See also page 438.

## WAXES

Waxes differ from fats and oils in that they are esters of various monohydroxy alcohols, instead of being confined to glycerol. The formulas of several waxes follow:

Spermaceti is largely cetyl palmitate,  $\text{C}_{15}\text{H}_{31}\overset{\text{O}}{\parallel}\text{C}-\text{OC}_{16}\text{H}_{33}$ .

Beeswax is cerotic acid,  $\text{C}_{25}\text{H}_{51}\overset{\text{O}}{\parallel}\text{C}-\text{OH}$ , with myricyl palmitate,



Chinese wax is ceryl cerotate,  $\text{C}_{25}\text{H}_{51}\overset{\text{O}}{\parallel}\text{C}-\text{OC}_{26}\text{H}_{53}$ .

Carnauba wax has been found to have a more complex composition than those already given. Inspection of these formulas shows these compounds to be quite analogous in structure to the simple esters which have already been studied.

The chemistry of the waxes resembles that of the simple esters, in so far as investigation has been made. Waxes are used in making candles, in toilet goods and cosmetics, in polishes, in textile sizing, in lacquers and varnishes, in electrical insulating mixtures, in candy making, and in medicine.

#### REVIEW QUESTIONS

- Write graphic formulas for: (a) Isopropyl acetate; (b) Butyl formate; (c) Methyl oleate; (d) Alkyl formate; (e) Amyl butyrate.
- Write the structural formulas of esters having the molecular composition  $\text{C}_6\text{H}_{10}\text{O}_2$ .
- Show by equations the formation of amyl nitrite; of amyl nitrate.
- Write equations for four methods of preparation of propyl acetate.
- Show in the form of a chart or table the reactions of acetyl chloride, acetic anhydride, and ethyl acetate, with water and with ammonia.
- Arrange the following substances in the order of their decreasing activity towards water: diethyl ether, acetic anhydride, ethyl acetate, acetyl chloride.
- In what way can it be shown that acetoacetic ester exists in both keto and enol forms?
- Show by equations how dimethylacetic acid may be made by the acetoacetic ester synthesis.
- Write equations showing how to make methyl isopropyl ketone by acetoacetic ester synthesis.
- What substances could be formed by aldol condensation between ethyl acetate and ethyl propionate? (Note remarks on page 149.)
- Write equation for the reaction of NaOH solution upon palmitin (Glycerol tripalmitate).
- How could sodium stearate be separated from stearin? From stearic acid?
- Show by equations the action of hard water (Ca, Mg ions) upon sodium palmitate.
- By what test could oleic acid be distinguished from stearic acid?
- Indicate by an equation the action of NaOH solution upon spermaceti.
- A compound of formula  $\text{C}_4\text{H}_8\text{O}_2$  was boiled with an excess of NaOH solution. In this way methyl alcohol and the compound  $\text{C}_3\text{H}_5\text{O}_2\text{Na}$  were formed. What was the original compound?
- How many cc. of N/10 NaOH solution are needed to completely saponify 10 g. of ethyl acetate?
- (R)18. With alcohol as a source of materials, make diisopropylacetic acid. All organic intermediate compounds are to be made from ethyl alcohol.

19. What analytical method shows that butter contains a larger quota of volatile fatty acids than does lard? Explain the method.
20. Calculate the saponification number of butyric (Glycerol tributyrate).
21. Why is soap an unsatisfactory cleaning agent when used in an acid solution?
22. What type of chemical compound is Igepon A? What long-chain organic acid is found in the molecule?
23. Suggest a method not shown in this chapter for the preparation of ethylidene diacetate.
24. How has it been decided that the alcohol loses hydrogen and the acid loses hydroxy group in an esterification?
25. A compound suspected of being either an ester or an acid anhydride is hydrolyzed. State the results which would follow: (a) if it were an acid anhydride; (b) if it were an ester.
26. How is it possible to distinguish an ester from a primary alcohol? from a ketone? Describe the tests to be used in each instance.
27. What test or tests would distinguish ethyl nitrite from nitroethane?
28. Is it possible to distinguish between a hard fat and paraffin wax? If so, how could it be done?
29. A soap may contain moisture or free fatty acid, or it may have uncombined alkali. Describe the procedure you would use to test for these three impurities.
30. Putty is made from chalk and linseed oil. Discuss the hardening of putty.
- (R)31. When the sodium salt of acetoacetic ester is treated with iodine, doubling of the molecule results. The new compound is hydrolyzed with base, and the resulting salt is treated with acid to liberate the organic acid product. This is then heated, whereupon it loses carbon dioxide. The final product is acetylacetone. Write a series of balanced equations for these changes. For what purposes is acetylacetone used?
32. If a mixture of acetic acid, hydrochloric acid, and ethyl alcohol is heated, ethyl acetate is formed; very little or no ethyl chloride appears. Use these facts in an explanation of the loss of OH by acid and H by alcohol in an esterification.
33. What yield of ester would be obtained by treatment of one mole of acetic acid (in presence of a small amount of sulfuric acid) with:
  - (a) four moles of ethyl alcohol;
  - (b) eight moles of ethyl alcohol;
  - (c) ten moles of ethyl alcohol?
 Plot the results on a curve and discuss them.
34. Define the following terms. (a) Drying oil; (b) Saponification; (c) Hydrogenation of oils; (d) Saponification number.
- (R)35. An unsaturated monocarboxylic acid whose molecular formula is  $C_2H_4O_2$  is treated as indicated below. Interpret the following equations.
  - (a)  $C_3H_4O_2 + HI \rightarrow (B)$ ;
  - (b)  $(B) + C_2H_5ONa$  (in excess)  $\rightarrow (C)$ ;
  - (c)  $(C) + C_2H_5I \rightarrow (D)$ ;
  - (d)  $(D) + NH_3 \rightarrow (E)$ .
 Name compound (E).
36. A sample of ethyl acetate weighing 4.4 g. was heated with 610 cc. of 0.1 N NaOH solution. How much of the NaOH solution remained unused?
- (R)37. An amide whose melting point is  $80 \pm 2^\circ$  gave upon treatment with nitrous acid an acid (A) which was treated with thionyl chloride to form the compound (B). Compound (B) was brought into reaction with ethyl alcohol to form (C) whose boiling point is about  $98^\circ C$ . Show the probable structure of (C) and of two of its isomers. Name the compounds.

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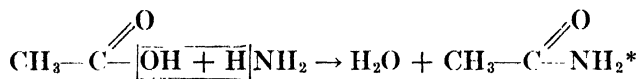
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## CHAPTER XI

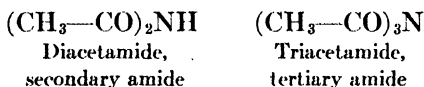
### ACID DERIVATIVES (III)

#### ACID AMIDES

The acid amides are C, H, O, N compounds, which are formed by the reaction of a fatty acid (acid anhydride, acyl halide) and ammonia. By this reaction, the OH group of the acid is replaced by NH<sub>2</sub>:



Amides may be looked at in two ways; they may be considered as derivatives of the acids (NH<sub>2</sub> substituted for OH), or as derivatives of ammonia formed by the substitution of acyl group for hydrogen. Pursuing the second conception further, we find that compounds exist in which two or all three hydrogen atoms of ammonia have been replaced by acyl groups. Such compounds are the secondary and tertiary amides:



Of the three groups of amides, the primary have the greatest importance, and they alone will receive attention here.

Amides (often called acid amides) have the type formula  $\text{R}-\text{C}(=\text{O})-\text{NH}_2^\dagger$  and are named directly from the acids by dropping the final "ic" from the name of the acid and adding "amide."

The newer names are formed from the name of the parent hydrocarbon and the ending "amide."



With the exception of formamide, which is a liquid, the primary amides are colorless solids. Acetamide, which is the most important, may be taken

\* This is generally printed CH<sub>3</sub>CONH<sub>2</sub> to save space; the student should, however, use the graphic formula when writing equations.

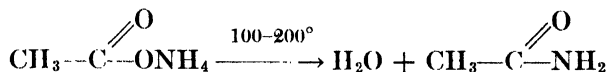
† The NH<sub>2</sub> group when attached to acyl is called *amido*; when in union with alkyl it is called *amino* group.

as a type. It is a hygroscopic, water-soluble compound, which unless specially purified, has an odor like mice.

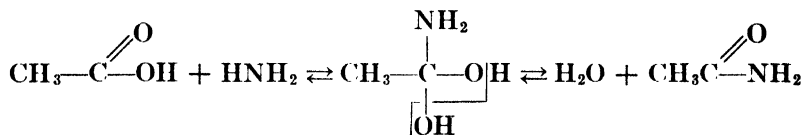
### PREPARATION OF AMIDES

Amides are formed by several distinct methods. The first four of those which follow are alike in theory, and represent the action of ammonia on an acid. These are:

(1) Heating the ammonium salt of an acid:



It may be supposed that the ammonium salt breaks down on heating, to give free ammonia and the acid (other ammonium salts do this). The following equation shows reactions which could then take place between these substances:

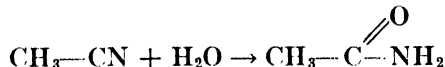


As aldehydes add ammonia, it is reasonable to suppose that the acids, which also have the carbonyl group, do likewise under the conditions imposed.

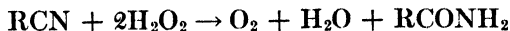
(2) Action of ammonia on the anhydride, acid halide, or ester of an acid. The equations are shown on pages 193, 189, and 206.

Alkyl-substituted amides are formed when amines are used for ammonia in this reaction (see page 310).

(3) The partial hydrolysis of a nitrile also yields an amide:

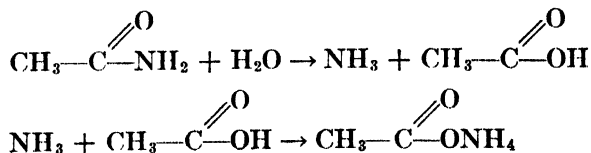


We have seen (page 164) that complete hydrolysis of nitriles results in the production of the corresponding acids. This partial hydrolysis may be accomplished by the use of a solution of hydrogen peroxide and sodium hydroxide, or with sulfuric acid:



### REACTIONS OF THE AMIDES

(1) *Action of water, hydrolysis:*

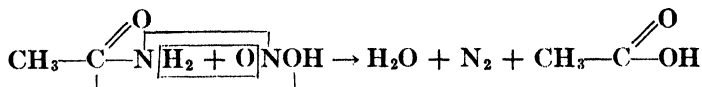




The use of either acid or base will cause this reaction to go to completion. In the one case the ammonia will form an ammonium salt with the acid; in the other the organic acid will be neutralized by the base.

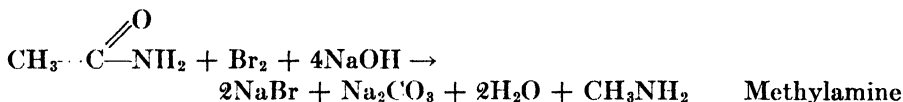
Attention should be drawn to the fact that all the substances which have been called "acid derivatives" including the salts, esters, anhydrides, halides, and amides, are subject to hydrolysis. The reaction of hydrolysis shown above is the reverse of that by which an amide is made from an ammonium salt.

(2) *Action of nitrous acid:*



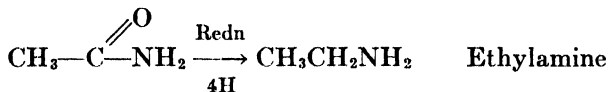
It will be found after study of the amines (page 311), that this is a typical reaction of  $\text{NH}_2$  group, forming a means of passing from  $\text{NH}_2$  to  $\text{OH}$ .

(3) *The Hofmann reaction, oxidation with sodium hypobromite.* Amides treated with bromine and sodium hydroxide solution yield amines having one less carbon atom.



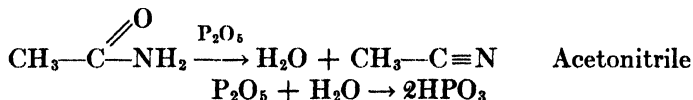
This reaction offers a means of shortening a carbon chain (see page 306) besides serving for the preparation of the primary amines.

(4) *Reduction of an amide, formation of an amine with the same number of carbon atoms.*

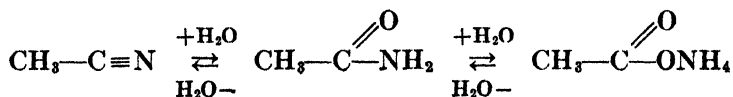


This reaction and the one just above illustrate that the amides and the compounds called amines are somewhat intimately related to each other. This point will be amplified in the chapter on amines.

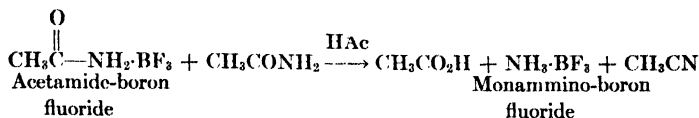
(5) *Dehydration of an amide, formation of a nitrile:*



We have seen that addition of water to a nitrile produces an amide. This reaction shows that the process is reversible. The relations of nitrile, amide, and ammonium salt are as follows:



A recent method for making nitriles involves the reaction between an amide and boron fluoride to make an addition compound. This compound in presence of acetic acid gives the nitrile and monammino boron fluoride:

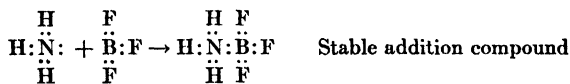


The yield of nitrile by this method is good. When treated with an alcohol the addition compound gives an ester in fair yield:



Boron fluoride may be regenerated to be used again by treating the ammonia complex with sulfuric acid. The acetamide complex is a good acetylating agent for cases in which the elements of ammonia can be eliminated.

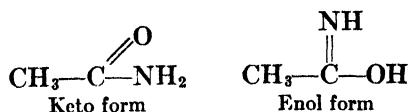
The compounds formed by boron fluoride with ammonia, acetamide, and other compounds of like nature are interesting in that their existence is predicted by the Lewis theory, but not by any previous theory. The electronic formulas of ammonia and boron fluoride show that the nitrogen of ammonia has a lone pair and that the boron has but six electrons in its outer shell. The needs of both atoms are satisfied when they come together:



The new compound contains a coördinate bond (see page 127) and its formula might be written  $\text{F}_3\text{B}^+\text{NH}_3^-$  to show that the nitrogen has made a contribution to boron.

(6) *Salt formation.* In water solution, the amides are neutral compounds, the basic character of the  $\text{NH}_2$  group being offset by the acid nature of the acyl radical. Towards reagents, they are amphoteric; they form salts with strong acids, which, however, are easily decomposed by water. With strong bases, salts are also formed. It seems probable that in the latter, the metal would be joined to oxygen rather than to nitrogen, but both structures are possible. An example of an amide salt is mercury acetamide,

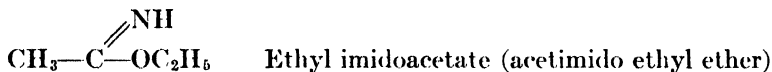
$(\text{CH}_3\text{C}(=\text{O})\text{NH})_2\text{Hg}$ , or  $(\text{CH}_3\text{C}(=\text{NH})\text{O})_2\text{Hg}$ , formed from the reaction of acetamide and mercuric oxide. Amides would then be tautomeric compounds, existing in two forms, one, the keto form, having a carbonyl group, while the other, the enol form,\* would have OH group:



This hypothesis is strengthened by the fact that derivatives of the enol form,

\* Keto-enol tautomerism is discussed on pages 145 and 209.

called imido esters (imido ethers), are known. Ethyl imidoacetate will serve as an example of this class of compounds.



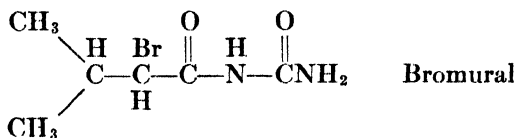
In no case have the two tautomeric forms of any aliphatic amide been separately isolated (see page 524). It appears likely from the behavior of amides that but little of the enol form is present under ordinary conditions.

(7) *Solvent powers.* Basing his conclusions on the many functions present in the acetamide molecule (hydrocarbon group, carbonyl, potential hydroxyl, amino, potential nitrile group) Stafford decided that it should be a good solvent for various types of compounds. The value of the graphic formula which allows this form of reasoning is self-evident. Trial has shown the soundness of the thesis and has led to an ever wider use of acetamide as a solvent.

TABLE 21.—ACIDS AND ACID DERIVATIVES

Radical	Carbons	Acid		Methyl ester		Ethyl ester		Amide		Acid chloride		Anhydride	
		M.p.	B.p.	M.p.	B.p.	M.p.	B.p.	M.p.	B.p.	M.p.	B.p.	M.p.	B.p.
Formic.....	1	8.6	100.8	-99.8	31.8	-79	54.0	2	193				
Acetic.....	2	16.7	118.1	-98.7	59	-82.4	77.1	81	222	-112.0	52	-73.0	139.6
								(69.4)					
Propionic.....	3	-22	141.1	-87.5	79.7	-72.6	99.1	79	213	-94	80	-45	168.00
Butyric.....	4	-4.7	163.5	<-95	102.3	-93.3	121.3	115	216	-89.0	102	-75.0	198.2
Valeric.....	5	-34.5	187.0		127.3		145.5	106	230		128		218
Caproic.....	6	-2.5	202		149.5		166.6	100	255		153.738		241
Enanthic.....	7	-10	223.5		172.0		187.1	96	258		175	+17	258-68
Caprylic.....	8	+16	237.5	-40	192.9	-44.8	207	105-10	>200		195	-1.0	285
									dec.				
Pelargonic.....	9	12.5	254		214	-44.5	227						
Capric.....	10	31.5	268.4	-18	224		245						
Undecylic.....	11	29-30	228.160					103					
Lauric.....	12	48	225.100	+5	148.18	-10.7	269	102	200.12.5	-17	145.18	41	166

**Hypnotics.** Neodorm, *alpha*-isopropyl-*alpha*-bromobutyramide, is an example of an amide hypnotic. Another bromine-containing hypnotic is called Bromural. Many other amide hypnotics have been made.



Inspection of Table 21, "Acids and acid derivatives," shows certain general facts about the relative boiling points. The acyl chlorides and ethyl

esters are seen to have lower boiling points than the acids, while the anhydrides and amides have higher boiling points than the acids.

### REVIEW QUESTIONS

- Write equations for four methods of preparing propionamide.
- Indicate by equations the action upon propionamide of: (a) NaOH solution; (b) HCl solution; (c)  $\text{HNO}_2$ ; (d)  $\text{Br}_2$  and KOH solution; (e) A reducing agent; (f) A dehydrating agent.
- Using acetamide as a source of materials show by equations how the following could be made from it: (a) Methane; (b) Acetic anhydride.
- (R)4. How may the following substitutions be brought about: (a)  $\text{C}-\text{OH}$  for  $\text{I}$ ? (b) OH for  $\text{NH}_2$ ? (c)  $\text{C}-\text{OH}$  for  $\text{C}-\text{NH}_2$ ? (d) H for  $\text{C}-\text{OH}$ ? (e)  $\text{NH}_2$  for  $\text{C}-\text{NH}_2$ ?
- Complete the following equations.
  - Butyryl chloride +  $\text{NH}_4\text{OH}$  solution  $\rightarrow$
  - Propionic acid +  $\text{NH}_4\text{OH}$  solution  $\rightarrow$
  - Propyl acetate +  $\text{NH}_4\text{OH}$  solution  $\rightarrow$
  - Acetamide +  $\text{Br}_2$  + NaOH solution  $\rightarrow$
  - Propionamide +  $\text{P}_2\text{O}_5 \xrightarrow{\Delta}$
  - Butyramide  $\xrightarrow[4\text{H}]{\text{Redn}}$
- How would you distinguish acetamide from ammonium acetate?
- Show by a series of equations the synthesis of acetamide from the elements.
- How many cc. of nitrogen will be produced by the action of nitrous acid upon 8 g. of acetamide? What weight of propionamide would yield this amount of nitrogen?
- If acetyl chloride reacts with butyramide what is formed? What compounds would result upon hydrolysis of the new substance with NaOH solution? If dilute sulfuric acid were used in the hydrolysis what compounds would form?
- Is the hydrolysis of an amide with either base or acid a reversible reaction? Is the hydrolysis of an ester with either base or acid a reversible reaction? Wherein lies the reason for the different actions reported in your answers to these questions?
- On what basis could you have predicted that amides would hydrolyze rather easily?
- What physical and chemical traits help to identify an amide?
- Write the graphic formula for Neodorm.
- Write a correct chemical name for Bromural.
- (R)15. In carrying out the following syntheses all necessary organic compounds are to be made from the compound indicated.
  - Synthesis of  $\text{CH}_3\text{CONH}_2$  from  $\text{CH}_3\text{OH}$ ;
  - Synthesis of  $\text{C}_2\text{H}_5\text{NH}_2$  from  $\text{HCOOCH}_3$ .
- A solid organic compound was analyzed with the following results: a sample weighing 0.125 g. gave 0.2260 g. of  $\text{CO}_2$  and 0.1079 g. of  $\text{H}_2\text{O}$ . The compound contains 21.92% oxygen; the balance is nitrogen. When treated with nitrous acid the compound reacted vigorously releasing a colorless gas. The resulting solution was found to contain an acid with a neutralization equivalent of 74. What was the original compound? Write equations showing how the original compound could be changed to propylamine.

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3. SOWA and NIEUWLAND. Organic reactions with boron fluoride. XIV. Reaction of amides with acids and amines. *J. Am. Chem. Soc.*, **59**, 1202 (1937). VI. Reaction of acetamide with alcohols and phenol. *J. Am. Chem. Soc.*, **55**, 5052 (1933).
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3. GALAT and ELION. The interaction of amides with amines. *J. Am. Chem. Soc.*, **65**, 1566 (1943).

## CHAPTER XII

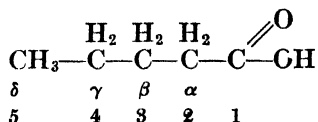
### SUBSTITUTED ACIDS

The substituted acids are compounds derived from the acids through replacement of alkyl hydrogen by various functions. The number of such substitutions possible is quite large, but in general we find our interest narrowed to three groups: the halogen acids, the hydroxy acids, and the amino acids. The last two named have important representatives in nature, while the first, the halogen acids, owe their importance to their usefulness in synthetic work.

This chapter will, therefore, treat of these three groups, beginning with the halogen acids, because they are easily made from the fatty acids themselves.

#### HALOGEN-SUBSTITUTED FATTY ACIDS

Our discussion will concern chiefly the chloro and bromo acids, although the iodo acids may also be made. All of the compounds in this group are laboratory products; before taking up the methods of their preparation, it is necessary to distinguish between the several different types of halogen acid. These are grouped according to the position which the substituted halogen holds with relation to the carboxyl group of the acid. The carbon atoms of the acid are named by letters of the Greek alphabet, beginning with the carbon atom *next the carboxyl group*:



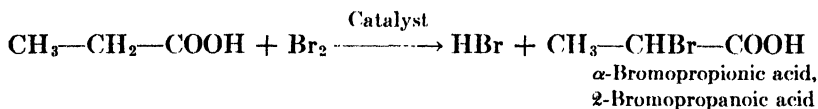
Thus we have *alpha*-, *beta*-, *gamma*-, etc., halogen acids. The end carbon of a chain is often termed *omega* ( $\omega$ ). An *omega* halogen acid would have halogen atom on the end carbon, regardless of the length of the chain. The use of numbers for the carbon atoms is also practiced. Examples of both systems of nomenclature will be shown.

#### PREPARATION OF HALOGEN-SUBSTITUTED ACIDS\*

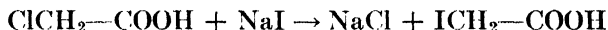
(1) The  $\alpha$ -acids (in some cases  $\beta$ -acids) may be prepared by the action of a free halogen upon an acid. The reaction ordinarily gives a mixture in

\* Halogen derivatives of formic acid are not known, although esters of chloroformic acid are stable compounds (page 260). The series properly begins with acetic acid.

which the *alpha* acid predominates, but can in certain instances be modified in the presence of catalysts so as to give predominantly the *beta* acids.

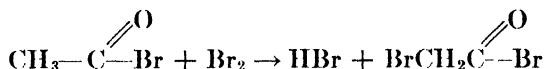


Iodo acids are made from chloro acids by treatment with a solution of sodium iodide in acetone.

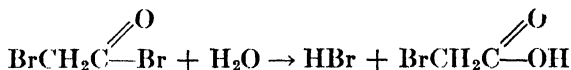


The action of halogen on a fatty acid takes place with greater ease with the higher acids than with those having short carbon chains. However, in general it is preferable to use the acid chloride (or anhydride) instead of the acid, as in this case the reaction may be carried out at a lower temperature and with much greater speed.

In making bromoacetic acid, red phosphorus, bromine, and acetic acid are allowed to react. The phosphorus bromide which forms on contact of phosphorus and bromine converts the acid to the acid bromide (page 187) which is then attacked by excess bromine:



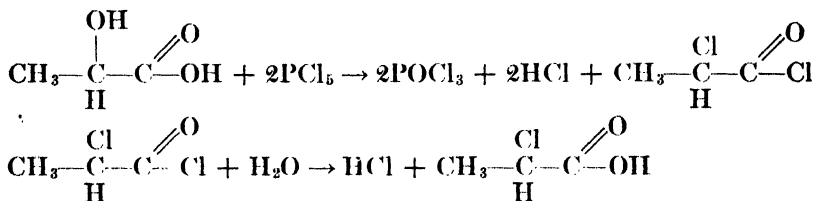
Hydrolysis of the brominated acid bromide yields the desired product:



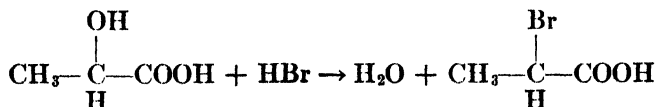
This is known as the **Hell-Volhard-Zelinsky reaction**.

(2) The halogen acids may usually be made from the corresponding hydroxy acids when these are available. The methods employed are those used to convert alcohols to alkyl halides (see Chapter IV).

(a) Formation from a hydroxy acid and phosphorus halide:



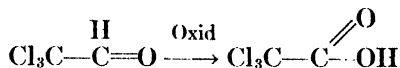
(b) Preparation by action of a halogen acid upon a hydroxy acid:



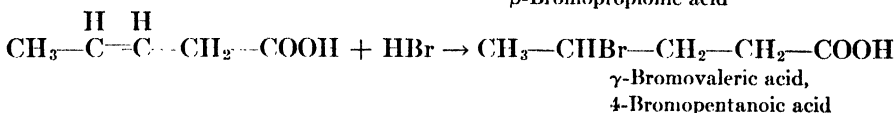
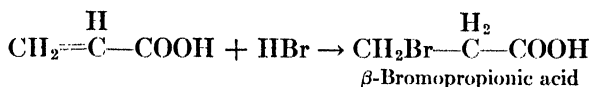
(3) In addition to the methods shown it is of course feasible to prepare halogen acids from the corresponding alcohol or aldehyde by oxidation:



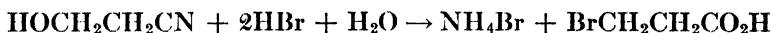
Trichloroacetic acid is easily prepared in this way from chloral:



The  $\beta$  and  $\gamma$  acids are made by the addition of hydrogen halide to an unsaturated organic acid. The halogen atom enters the molecule as far as possible from the carboxyl group. This is what we would expect if there is a drift of electrons toward the carboxyl group as was proposed in Chapter VIII.



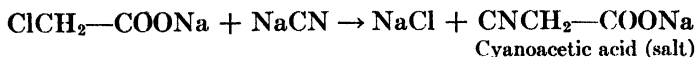
Iodo acids are made by the use of hydrogen iodide in this reaction. A neat synthesis of  $\beta$ -bromopropionic acid involves simultaneous action upon hydroxyl and nitrile groups:



#### REACTIONS OF HALOGEN ACIDS

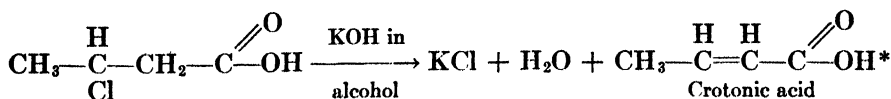
These compounds present themselves both as acids and as alkyl halides. As acids they form all of the normal derivatives, salts, esters, etc., with which we are already familiar, and which will need no further discussion. The reactions which follow are common to the alkyl halides as may be seen by a comparison of these equations with those on page 82.

(1) *Reaction with sodium cyanide; formation of a cyano acid:*



The cyano acid by hydrolysis yields a dicarboxylic acid; this reaction thus gives a method of passing from mono- to dicarboxylic acids. (See page 251.)

(2) *Formation of an unsaturated acid by action of alcoholic potash on a halogen acid:*



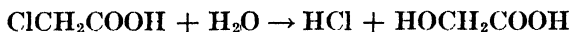
\* The treatment of a carboxylic acid with a base results in the immediate neutralization of



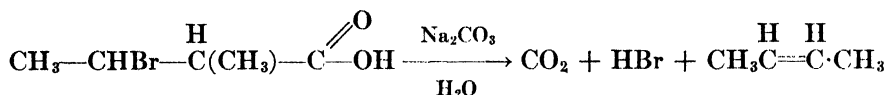
The  $\beta$ -halogen acids are especially reactive in this respect, only requiring in some cases to be boiled with water to cause loss of halogen acid.

(3) *Hydrolysis, ammonolysis.* See pages 238, 244.

**Effect of Halogenation on Reactivity.** (a) *Exchange of Cl for OH.* The effect of halogenation on the strength of acids has already been noted (page 171). The presence of carboxyl is also found to render the halogen more "sensitive," that is, alkyl halide type reactions which normally proceed only at high temperatures or slowly, take place readily with the halogenated acids. Thus, in the action of water on  $\alpha$ -halogen acids the exchange of halogen for OH takes place much more readily than in the change from alkyl halide to alcohol:



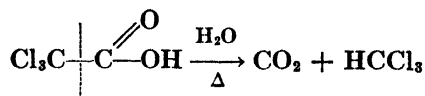
*Beta* halogen acids also readily exchange halogen atoms for hydroxyl when warmed with water. The main reaction product however, is an unsaturated acid (see above equation). The use of sodium carbonate may cause the loss of carbon dioxide from the acid, yielding an *unsaturated hydrocarbon*:



We have seen that salts of saturated acids lose carbon dioxide when fused with alkali (page 28). Certain *beta* halogen acids, however, undergo this type of reaction at a much lower temperature, and in presence of water. The reaction occurs with some  $\alpha$ ,  $\beta$ -halogen acids and with  $\alpha$ -alkyl- $\beta$ -halogen acids.

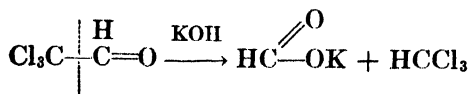
*Gamma* and *delta* halogen acids yield hydroxy acids quite easily when heated in water solution, and these then lose a molecule of water to form lactones (page 241).

(b) *Loss of carbon dioxide.* The presence of carboxyl evidently increases the activity of the halogen atom by rendering its attachment to carbon less secure. When several halogen atoms are found on one carbon, this reactivity appears to pass to the carbon itself; thus when trichloroacetic acid is heated in aqueous solution, the two carbons are separated. Chloroform is produced:

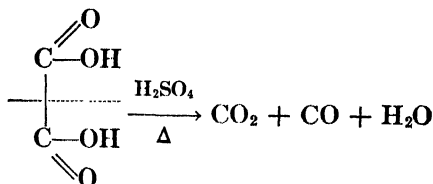


the carboxyl group, and the subsequent reaction then takes place with the *salt* of the acid. At the close of this second reaction the salt by treatment with a mineral acid reverts to a carboxy compound. Equations which take up reactions of acids with basic reagents generally omit mention of the salt formation since it has nothing to do with the business in hand. It is, however, important from two sides: first it introduces an extra step of synthesis, i.e., the final treatment with mineral acid; second, one uses *twice* as much base as is shown in the equation.

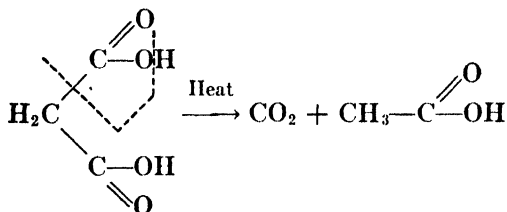
Examples of similar reactions in compounds having two negative groups close together are found in the decomposition of chloral:



of oxalic acid:



of malonic acid (page 254):



of acetoacetic ester (page 211), etc.

We may suppose that the drift of electrons toward the negative atoms at the ends of these chains is responsible for the weakening of the C—C bond.

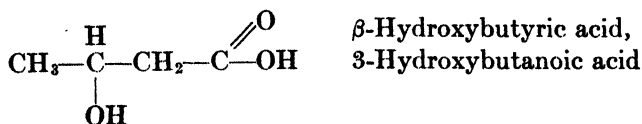
#### USES OF HALOGEN ACIDS

The chief use of compounds of this series is for the synthesis of other compounds. Thus chloroacetic acid is used to make malonic acid (page 251) and indigo (page 694). Trichloroacetic acid has a limited use in medicine for the removal of warts and other small growths.

#### HYDROXY ACIDS

Hydroxy acids, as their name implies, have OH group substituted for alkyl hydrogen. These compounds show at the same time the character of acids and of alcohols. The position of the OH group is indicated by the Greek letters *alpha*, *beta*, *gamma* ( $\alpha$ ,  $\beta$ ,  $\gamma$ ) etc., counting off from the carboxyl group, as for the halogen acids. The numbering system is also used.

Example:



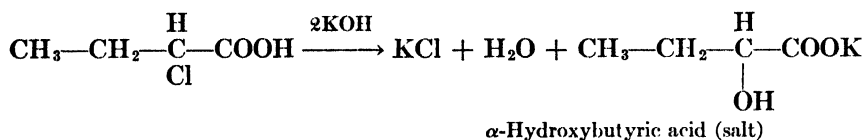
Many hydroxy acids are found in nature in the plants and fruits. The group includes compounds with one, two, or more OH groups, also mono-, dicarboxylic acids, etc. The monocarboxylic acids will be discussed here. For dicarboxylic acids, see page 249.

#### PREPARATION OF MONOCARBOXYLIC HYDROXY ACIDS

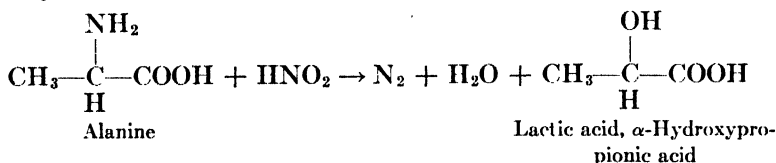
There are two **general methods of preparation** for these compounds: (1) either the OH group may be introduced into an acid, or (2) the carboxyl group may be brought into an alcohol molecule. In either case the methods employed are those with which we are already familiar from our study of alcohols and acids. They will be repeated for the benefit of review.

(1) *Introduction of OH Group into an Acid.*

(a) By treatment of a halogen acid with water or a base:



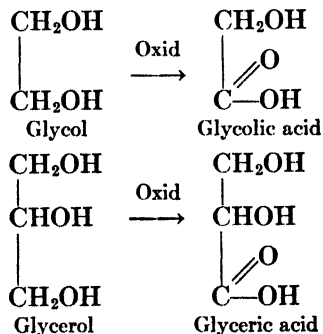
(b) By action of nitrous acid on an amino acid:



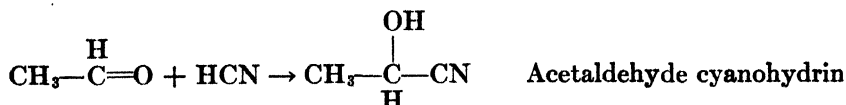
This reaction should be compared with that on page 228 showing the action of nitrous acid on amides. Also see amines, page 311, and page 715.

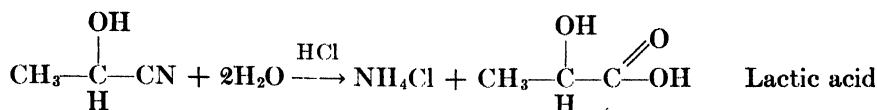
(2) *Introduction of Carboxyl Group into an Alcohol.*

(a) By the partial oxidation of a polyalcohol:

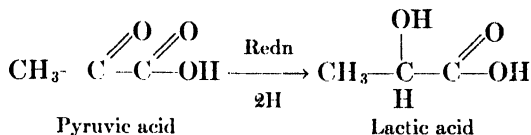


(b) By the hydrolysis of a cyanohydrin:

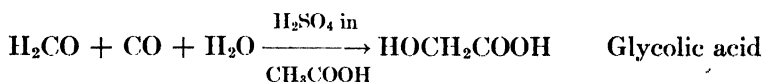




A special method for the production of a hydroxy acid involves the careful reduction of a keto acid:



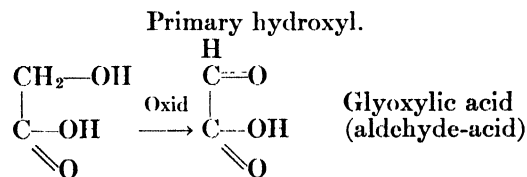
Glycolic acid is made by reaction of formaldehyde, carbon monoxide, and water, under pressure, at 160–170°:



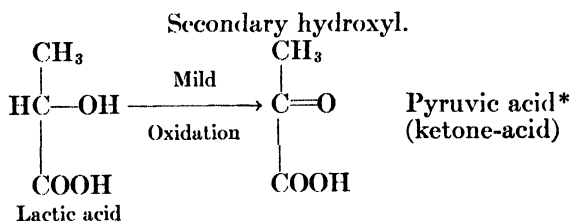
#### REACTIONS OF MONOCARBOXYLIC HYDROXY ACIDS

All of the normal reactions of acids and alcohols belong to the hydroxy acids. The products of oxidation vary according to whether the OH group is located on primary, secondary, or tertiary carbon, as with the alcohols.

Examples:

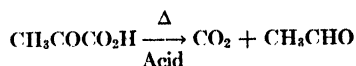


Glycolic acid



Lactic acid

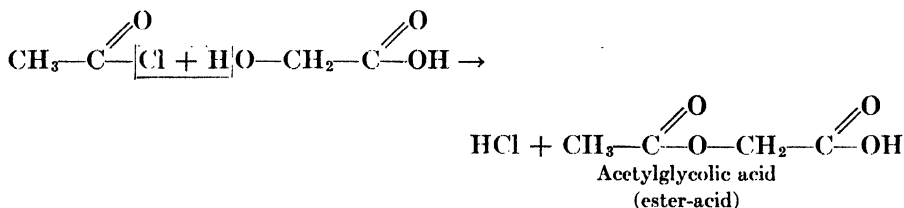
\* Pyruvic acid easily loses carbon dioxide to give acetaldehyde:



Thus this sequence gives us a method of passing from lactic acid to the next lower aldehyde. The change is brought about with lactic acid also, either by use of a strong oxidizing agent

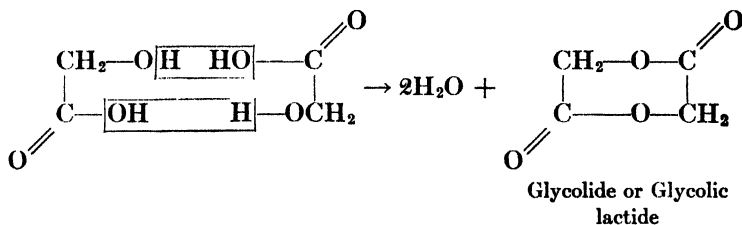
Salts, esters, etc., are formed from the carboxyl group. Metallic sodium replaces hydrogen from both hydroxyl groups. Esters and ethers are produced from interaction of hydroxyl group in precisely the same fashion as with an alcohol.

Example of ester formation by hydroxyl group:



**Water-removing Reactions.** Carboxylic acids normally react with alcohols to form esters; when both carboxyl and hydroxyl groups are contained *within the same molecule*, several new possibilities arise and new types of compounds are formed.

(a) *Alpha* hydroxy acids form ring compounds called *lactides* by interaction of two molecules, the carboxyl group of one forming an ester with the hydroxyl of the other and vice versa.



The compound formed is a cyclic ester. Like an ordinary ester with an open carbon chain, this substance may readily be hydrolyzed and glycolic acid reformed.

(b) *β*-hydroxy acids on being heated lose water to give *α, β*-unsaturated acids.

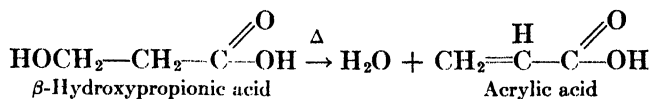
or of concentrated sulfuric acid. Other *alpha* hydroxy acids behave similarly, giving aldehydes or (if the chain branches at the carbon holding hydroxyl group), ketones.

The reactions may be used in determining the structure of an unknown acid. The sequence of reactions would be:

- (a) Bromination to produce an *α*-bromo acid,
- (b) Transformation to the *α*-hydroxy acid,
- (c) Oxidation to produce an aldehyde with loss of one carbon atom,
- (d) Oxidation of this aldehyde to its acid,
- (e) Bromination, etc.

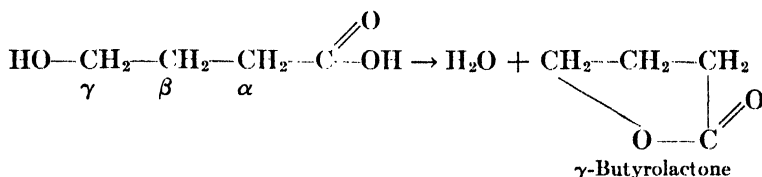
This process is repeated until the aldehyde or ketone which results is a known compound.

Example:

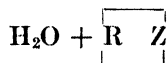


(c) The carboxyl group of a hydroxy acid will form an ester with the OH group of the same molecule if the two groups are separated by at least two carbon atoms (Baeyer strain theory, page 610). Such internal esters are called *lactones*.

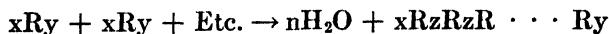
Example:



*Discussion.* This type of reaction readily occurs when the ring formed has five or six atoms. If the ring to be formed has seven or more atoms, the reaction usually is between separate molecules. If we represent a hydroxy acid as xRy, x and y standing for HIO and COOH, then in cases in which a five- or six-atom ring can form, we secure:



but for rings of seven or more atoms a polymerization occurs, giving molecular chains of various lengths, whose average molecular weight is usually high:



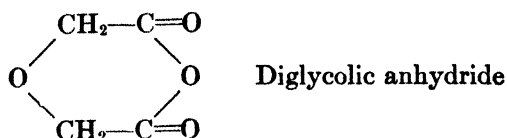
By low pressure distillation of such a mixture of polymers it is possible to

secure  $\boxed{\text{R} \quad \text{Z}}$  type compounds with large rings.

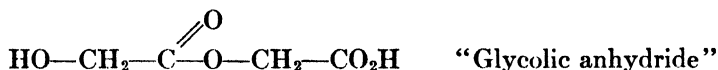
The thoughtful student will have seen that there are other possibilities besides those mentioned for loss of water between molecules of a hydroxy acid. Glycolic acid, for instance, may form an ether-acid:



an ether anhydride:



and a simple ester:



**Summary of Reactions.** *Alpha Hydroxy Acids.* Form lactides easily. On gentle oxidation give keto acids. On strong oxidation or treatment with sulfuric acid, give lower aldehydes or ketones.

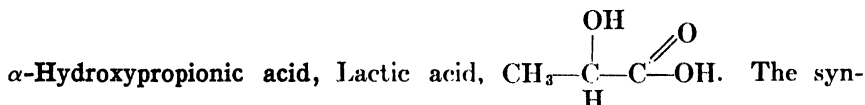
*Beta Acids.* Lose water readily to give  $\alpha$ ,  $\beta$ -unsaturated acids.

*Gamma and Delta Acids.* Easily yield lactones.

#### MONOCARBOXYLIC HYDROXY ACIDS

**Hydroxyformic acid**,  $\text{HO}-\text{CO}_2\text{H}$  (carbonic acid) is not capable of isolation. It probably exists in water solution, however. Its derivatives are described in the chapter on dicarboxylic acids (page 260).

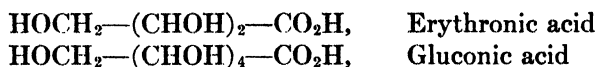
**Hydroxyacetic acid**, Glycolic acid,  $\text{HOCH}_2\text{CO}_2\text{H}$ , is found in unripe grapes. Its oxidation yields oxalic acid, as is indicated in the scheme on page 110.



thesis of this compound is shown on page 238. Lactic acid is produced in nature by the action of certain species of bacteria on milk sugar, also by the “souring” of other food products, such as sauerkraut. The **commercial method of preparation** is the fermentation of corn sugar, molasses, or lactose. It is normally present in the stomach and in the muscular tissue. The molecule of lactic acid contains an asymmetric carbon atom; therefore there are several different forms of this compound, as we shall find when studying the subject of optical activity. Lactic acid is used in the leather industry, in foods, beverages, and candies; as a plasticizer in synthetic resins.

**$\beta$ -Hydroxypropionic acid**,  $\text{HOCH}_2\text{CH}_2\text{CO}_2\text{H}$ , is also known but has not the importance of lactic acid.

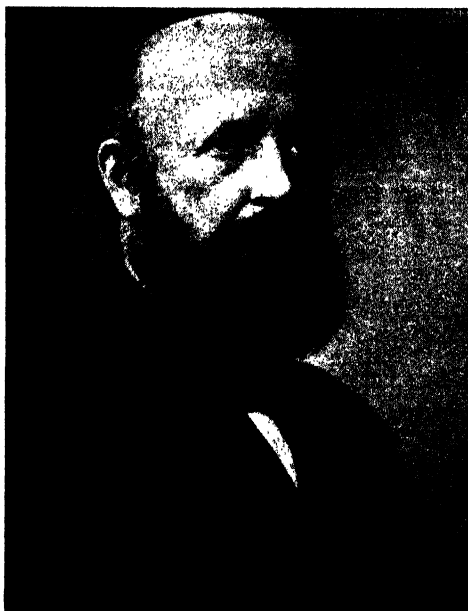
**Glyceric acid**,  $\text{HOCH}_2\text{CH}(\text{OH})\text{CO}_2\text{H}$ , whose formation from glycerol has been shown, is an example of a dihydroxy monocarboxylic acid. Other polyhydroxy alcohols will, like glycerol, yield monocarboxylic hydroxy acids on careful oxidation. Substances such as the following result:



#### AMINO ACIDS

These compounds are acids in which hydrogen of the alkyl group has been substituted by the amino group ( $\text{NH}_2$ ). They are not to be confused with amides in which  $\text{NH}_2$  is substituted in the carboxyl group (page 226). The

ADOLPH VON BAEYER (Johann Friedrich Wilhelm). (1835–1917, German.) Outstanding worker in theory and synthesis. Best known for his work with indigo. The structure was proved and many different methods of synthesis were perfected. Baeyer's strain theory is well known to students. He received the Nobel prize in 1905. See *J. Chem. Soc. (London)*, **123**, 1520 (1923), *J. Chem. Education*, **6**, 1381 (1929), *ibid.*, **7**, 1231 (1930); also this book, pages 280, 610.



RUDOLPH FITTIG. (1835–1910, German.) Professor of chemistry at Strassburg. Noted for synthetic work in the aromatic series. See *J. Chem. Soc. (London)*, **99**, 1651 (1911); also this book, pages 405, 585.

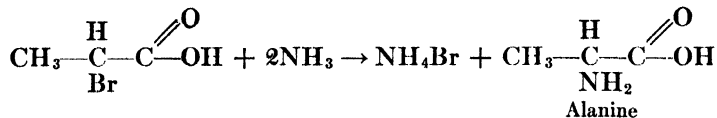
*Berichte* **44**, 1559 (1911).



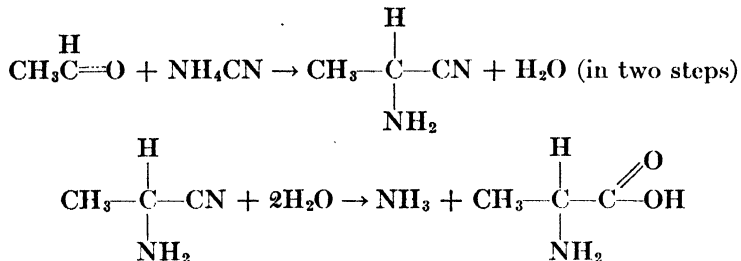
$\alpha$ -amino acids are natural products, in that they result from the hydrolysis of the proteins. (See page 715.)

### PREPARATION OF AMINO ACIDS

(1) Formation from a halogen acid and ammonia:



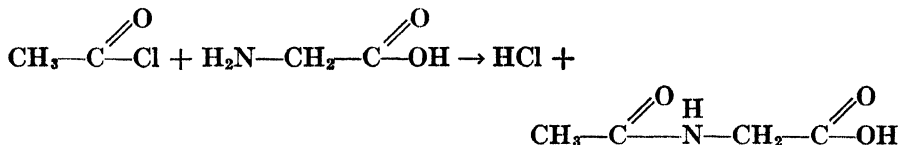
(2) Preparation from the action of ammonium cyanide ( $\text{NH}_4\text{Cl} + \text{KCN}$ ) upon an aldehyde; the **Strecker reaction**.



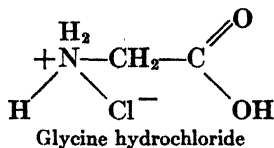
This reaction produces  $\alpha$ -amino acids only. Further material on preparation of amino acids is given in Chapter XXXVII.

### REACTIONS OF AMINO ACIDS

The amino acids share all of the general reactions of acids and primary amines. Esters, salts, and other acid derivatives are formed by action of the carboxyl group. The amino group may be replaced by OH in the usual manner by treatment with nitrous acid (page 238); acyl halides react with amino acids as with ammonia, forming in this instance substituted amides which also are acids.

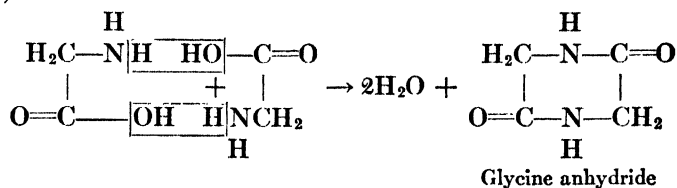


The basic character of the  $\text{NH}_2$  group comes into play when the acidic nature of carboxyl has been masked, as in the esters; moreover the amino acids themselves form salts like the following with strong mineral acids.

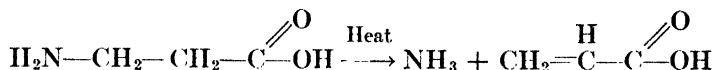


They also form internal salts as shown in the following discussion.

Certain reactions of the amino acids bear a strong resemblance to those of the hydroxy acids. Thus, an  $\alpha$ -amino acid on being heated, forms a ring compound, similar to a lactide, by loss of two molecules of water (see page 725).

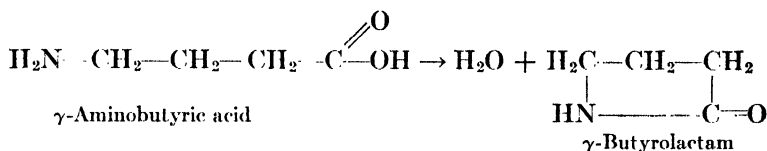


Likewise,  $\beta$ -acids, on being heated, lose ammonia to form unsaturated acids:



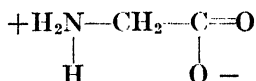
Gamma acids lose water to form internal amides called *lactams*.

Example:

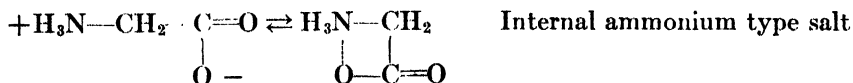


Here again the type of reaction is similar to that of a hydroxy acid.

**Internal Salt Formation, Zwitterions.** Amino acids, such as glycine, give practically neutral water solutions. This is probably not due to a failure of the molecule to ionize. It is more likely that the nitrogen has taken a proton (see discussion, page 715) and the carboxyl has lost one, both of these actions being typical for these groups. The resulting ion is a hybrid neutral ion called a dipolar ion or zwitterion:\*



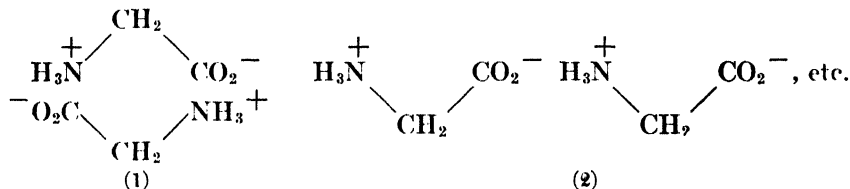
Remembering that the four-atom chain  $\text{N}-\text{C}-\text{C}-\text{O}$  is actually bent, due to the valence angles between the N, C, C, and O, we see that the terminal N and O are actually quite near each other, and it would be possible for the ion to pass to an *inner salt* by attraction between O and N:



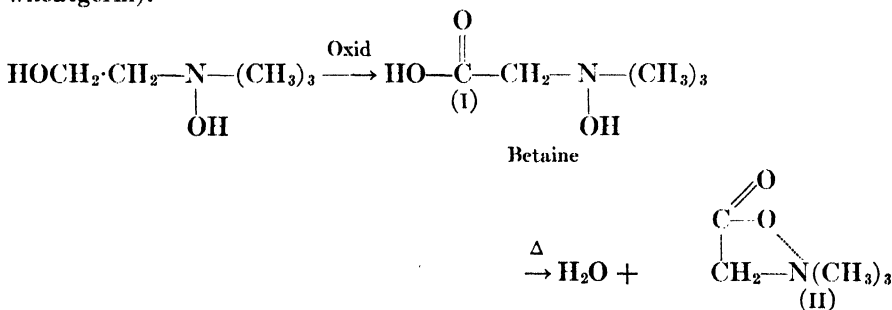
Such a salt would, of course, not affect the *pH* of water. A water solution of amino acid may then be supposed to contain neutral ions as shown above, in equilibrium with a small number of neutral "inner salt" molecules. In

\* Further evidence to support this conclusion is given in the chapter on proteins.

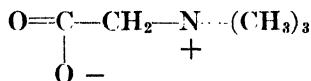
the solid state the zwitterions are held together by the electrostatic attraction between the opposite charges of neighboring units; the situation is similar to that in an inorganic salt (page 14). Two arrangements are exhibited by glycine, one in which the molecules are in pairs (1), another in which they form chains of indeterminate length (2).



**Betaine.** The compound choline (page 314) gives by oxidation a methylated glycine known as betaine (found in beetroot, cottonseed, wheatgerm).



The compound crystallizes as the hydroxide shown at (I), but easily loses water when heated to 100° to give a salt-like derivative with a high melting point (293°) possibly with the structure shown at (II). A molecule like (II) would split in water to give a neutral ion:



such as we have pictured above for a simple amino acid.

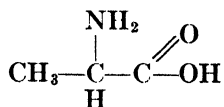
Betaine is prepared synthetically from trimethylamine and chloroacetic acid; its **commercial source** is sugar beet molasses.

#### AMINO ACIDS

**Aminoformic acid, carbamic acid,**  $\text{H}_2\text{N}-\overset{\text{O}}{\parallel}{\text{C}}-\text{OH}$ , is known only in its salts and esters, the latter being the urethans (page 261). Here again, we have a series in which the first member cannot be isolated.

**Glycine, glycocoll, or aminoacetic acid,**  $\text{H}_2\text{N}-\text{CH}_2-\overset{\text{O}}{\parallel}{\text{C}}-\text{OH}$ .

**Alanine,  $\alpha$ -aminopropionic acid, 2-aminopropanoic acid,**



Further information about amino acids will be found in the chapter on proteins.

### REVIEW QUESTIONS

- Write equations for two methods of preparation for: (a)  $\alpha$ -chlorobutyric acid; (b)  $\alpha,\beta$ -Dichloropropionic acid.
- Show by equations how  $\alpha$ -chlorobutyric acid may be formed from  $\alpha$ -hydroxybutyric acid.
- Write equations for the preparation of  $\beta$ -chloropropionic acid; for  $\gamma$ -bromobutyric acid.
- (R) 4. Outline the method by which malonic acid is made from acetic acid.
- Write equation for the formation of butylene from  $\alpha$ -methyl- $\beta$ -bromobutyric acid.
- Write equations for three methods of preparing hydroxyacetic acid.
- Show by equations how propionaldehyde may be used to make  $\alpha$ -hydroxybutyric acid.
- Write equations for the reaction of  $\alpha$ -hydroxybutyric acid with: (a)  $\text{PCl}_5$ ; (b) Acetyl chloride; (c)  $\text{NaOH}$  solution; (d) Sodium.
- Show by equations the types of reaction which distinguish *alpha*, *beta*, and *gamma* hydroxy acids.
- Write equations for two methods of preparing *alpha*-aminobutyric acid.
- Show the reaction of the above compound with: (a)  $\text{HNO}_2$ ; (b) Acetyl chloride.
- Write equations to show the reactions which distinguish *alpha*, *beta*, and *gamma* amino acids.
- Give the tests by which the following could be distinguished from each other:
 

(a)  $\text{CH}_2\text{Br}-\text{C} \begin{array}{l} \nearrow \text{O} \\ \searrow \text{OH} \end{array}$  and  $\text{CH}_3-\text{C} \begin{array}{l} \nearrow \text{O} \\ \searrow \text{Br} \end{array}$ ; (b)  $\text{NH}_2-\text{CH}_2-\text{C} \begin{array}{l} \nearrow \text{O} \\ \searrow \text{OH} \end{array}$  and  $\text{CH}_3-\text{C} \begin{array}{l} \nearrow \text{O} \\ \searrow \text{NH}_2 \end{array}$ .
- Given  $\text{CH}_3-\text{CH}_2-\text{C} \begin{array}{l} \nearrow \text{O} \\ \searrow \text{OH} \end{array}$  how could the following compounds be made from it:
 

(a)  $\text{CH}_3-\text{CHBr}-\text{C} \begin{array}{l} \nearrow \text{O} \\ \searrow \text{OH} \end{array}$ ? (b)  $\text{CH}_2\text{OH}-\text{C} \begin{array}{c} \text{H} \\ | \\ \text{C} \begin{array}{l} \nearrow \text{O} \\ \searrow \text{OH} \end{array} \end{array}$ ? (c)  $\text{CH}_2=\text{C} \begin{array}{c} \text{H} \\ | \\ \text{C} \begin{array}{l} \nearrow \text{O} \\ \searrow \text{OH} \end{array} \end{array}$ ?

(d)  $\text{CH}_2\text{I}-\text{CH}_2-\text{C} \begin{array}{l} \nearrow \text{O} \\ \searrow \text{OH} \end{array}$ ?
- Which is the stronger acid, lactic acid or  $\beta$ -hydroxypropionic acid? Why?
- What analytical tests distinguish between an acid chloride and a chloro acid? Describe how the tests are made and write equations for the chemistry involved.
- Which type of substituted acid responds to a test with nitrous acid? How is the test made? What indicates a positive test?
- How many moles of normal sodium hydroxide solution would be required to neutralize one mole of lactic acid?
- Would metallic sodium react with sodium lactate? In what way?
- Construct a chart to show medical uses of compounds discussed in this chapter.
- Indicate by series of complete equations how the following conversions may be brought about.
 

(a)  $\beta$ -Hydroxypropionic acid from glycerol;  
 (b) Trichloroacetic acid from methanol;  
 (c) Lactic acid from ethanol.
- Give facts which justify the structure assigned to lactic acid.

23. A 0.25 g. sample of a certain amino acid gave 62.9 cc. of nitrogen gas (N.T.P.) when treated with nitrous acid. What is its molecular weight? On what carbon atom is the amino group situated? If the data given do not supply an answer to this question, what work should be done with the compound to furnish the answer?

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# CHAPTER XIII

## DICARBOXYLIC ACIDS

As the name implies, the polycarboxylic acids contain several atoms of hydrogen replaceable by metals; that is to say they have several carboxyl groups. The most important of these acids are those with normal chains of carbon atoms and with two carboxyl groups. These acids are colorless solids which crystallize well. A peculiarity which appears on inspection of the accompanying table is that acids which contain an even number of carbon atoms have melting points higher than those of the next following acids which have odd numbers of carbon atoms. Also the solubility in water is greater for the acids with odd numbers of carbon atoms. These facts are not as yet explained, but it is likely that both properties are conditioned by the interatomic forces in the crystals, and that these forces are greater in the acids with an even number of carbon atoms. The table on page 163 shows a similar peculiarity in the melting points of the monocarboxylic saturated acids.

TABLE 22.—DICARBOXYLIC ACIDS

Names	Formula	M.p., °C.	B.p., °C.	Sp. g., 15°/4°	Ht. of comb.	Parts sol. in 100 parts H <sub>2</sub> O
Oxalic acid.....	(CO <sub>2</sub> H) <sub>2</sub>	186-7 dec. 101.5 (2H <sub>2</sub> O)	.....	1.053 <sup>19</sup>	60.15	10.2 <sup>20</sup>
Malonic acid, Propanedioic acid...	CH <sub>2</sub> (CO <sub>2</sub> H) <sub>2</sub>	130-5 dec.	.....	1.631	207.2	138 <sup>16</sup>
Succinic acid, Butanedioic acid....	(CH <sub>2</sub> ) <sub>2</sub> (CO <sub>2</sub> H) <sub>2</sub>	189-90	235	1.562	357.1	6.8 <sup>20</sup>
Glutaric acid, Pentanedioic acid...	(CH <sub>2</sub> ) <sub>3</sub> (CO <sub>2</sub> H) <sub>2</sub>	97.5	200 <sup>20</sup>	1.429 <sup>15</sup>	514.8	65.9 <sup>20</sup>
Adipic acid, Hexanedioic acid.....	(CH <sub>2</sub> ) <sub>4</sub> (CO <sub>2</sub> H) <sub>2</sub>	151-3	265 <sup>100</sup>	.....	668.8	1.44 <sup>16</sup>
Pimelic acid, Heptanedioic acid....	(CH <sub>2</sub> ) <sub>5</sub> (CO <sub>2</sub> H) <sub>2</sub>	103-5	272 <sup>100</sup>	1.329	.....	2.5 <sup>14</sup>
Suberic acid, Octanedioic acid.....	(CH <sub>2</sub> ) <sub>6</sub> (CO <sub>2</sub> H) <sub>2</sub>	140-4	279 <sup>100</sup>	.....	985.2	0.142 <sup>15,5</sup>
Azelaic acid, Nonanedioic acid.....	(CH <sub>2</sub> ) <sub>7</sub> (CO <sub>2</sub> H) <sub>2</sub>	106.5	286.5 <sup>100</sup>	1.029 <sup>20</sup>	1141.4	0.2 <sup>20</sup>
Sebacic acid, Decanedioic acid.....	(CH <sub>2</sub> ) <sub>8</sub> (CO <sub>2</sub> H) <sub>2</sub>	134.5	294.5 <sup>100</sup>	.....	1297.3	0.1 <sup>17</sup>

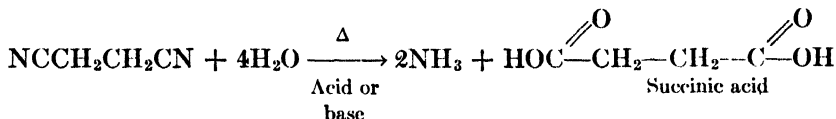
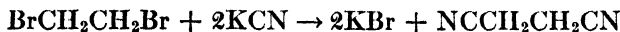
**Occurrence, Uses.** Like the monocarboxylic acids the dicarboxylic\* are well distributed in nature. Oxalic acid, which has been known for about 300 years, is found in rhubarb, sorrel, and certain other plants, usually as the calcium or the acid potassium salt. Malonic acid is found in beet root in the form of the calcium salt. Succinic acid may be obtained from amber by distillation. The dicarboxylic acids are valuable from the synthetic standpoint; in addition there are many special uses for individual members.

\* The name dicarboxylic is more exact than dibasic, but the latter is widely used in the literature, presumably because it is more familiar.

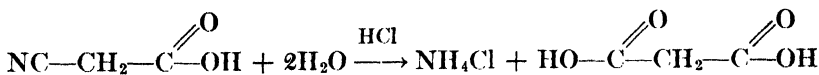
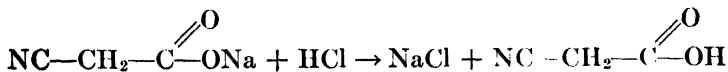
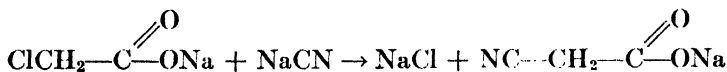


nia water. At that time oxalic acid was considered to be an inorganic compound; hence Wöhler placed no great importance on its production, but, like other chemists of the time, laid emphasis only on the synthesis of the urea. The fact is, however, that in one and the same reaction Wöhler formed both a vegetable and an animal compound from an inorganic compound, disproving absolutely the necessity for "vital force." The following method of synthesis is more generally applicable.

(3) The reaction of a dihalogen compound with potassium cyanide produces a dicyanide; this on hydrolysis gives a dicarboxylic acid:

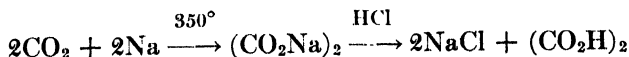


The above reaction may also be utilized to form malonic acid from acetic acid:



In practice the diethyl ester is made rather than the free acid. This is accomplished by heating the salt of malonic acid with alcohol and sulfuric acid, or by subjecting sodium cyanoacetate to treatment with alcohol and a mineral acid.

(4) Oxalic acid may be made by the action of carbon dioxide upon metallic sodium, a method which recalls the formation of formic acid from carbon monoxide and sodium hydroxide (page 174).

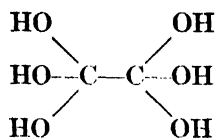


(5) We have seen that oxalic acid may be made from formic acid through heating of its alkali salts (page 176). This is an important technical method of preparing oxalic acid. Oxalic acid is not readily oxidized by nitric acid; it is therefore obtained as a final product of reaction when sugars, starches, or cellulose are oxidized with this reagent. These molecules contain  $-\text{CHOH}-\text{CHOH}-$  groups which are split from them in the serious decomposition induced by nitric acid, and oxidized to oxalic acid.

(6) Oxalic acid has been made commercially by treatment of sawdust or shavings with sodium- and potassium hydroxide solution at an elevated



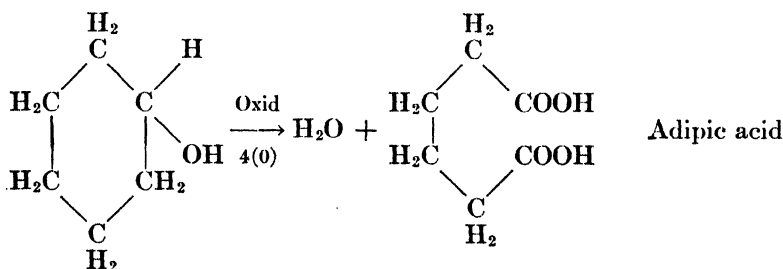
temperature. Addition of lime precipitates calcium oxalate, from which crude oxalic acid is secured, to be purified by recrystallization. Oxalic acid crystallizes with two molecules of water which are probably held as shown here:



This retention of several hydroxyl groups by one carbon recalls the behavior of chloral. We find it in compounds with strongly negative groups. The acid may be dehydrated by heating to a temperature of about 100°.

**Succinic acid** is made commercially by electrolytic reduction of maleic or fumaric acid.

**Adipic acid**, a necessary intermediate for the production of Nylon, is made by the oxidation of cyclohexanol (page 499).



### NOMENCLATURE

The common names of dicarboxylic acids are adapted from names of botanical and other natural sources.

Name	Source
Oxalic.....	Sorrel (Oxalis)
Malonic.....	From malic acid
Succinic.....	From amber (Succinum)
Glutaric.....	From gluten
Adipic.....	From fat (Adeps)
Pimelic.....	From fat (Greek, Pimele)
Suberic.....	From cork (Suber)

The official names of the acids (except oxalic) are taken from the name of the hydrocarbon of like carbon content, with the suffix "dioic acid":



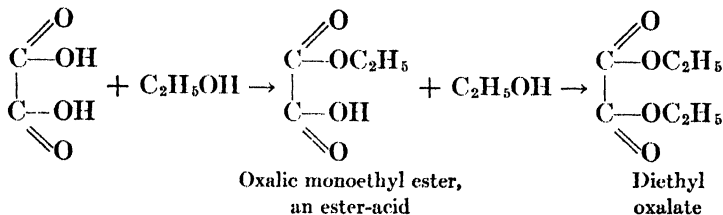
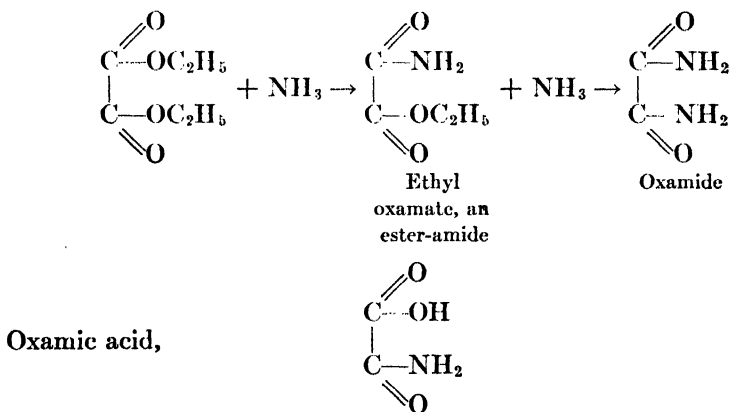
or else are formed by considering the carboxyl groups as having been substituted for hydrogen of a saturated hydrocarbon:



## REACTIONS OF DICARBOXYLIC ACIDS

All of the normal reactions of the fatty acids belong to the dicarboxylic acids. In addition, a dicarboxylic acid can use one or both of its carboxyl groups, thus forming two classes of derivatives in a given case where only one would be possible for a monocarboxylic acid.

Examples:

(1) *Ester formation:*(2) *Amide formation:*

which combines the functions of an acid and an amide, and other mixed derivatives are also known. In subsequent pages we shall frequently meet with "mixed compounds" like the above examples, which belong simultaneously to different chemical series. Their reactions are always varied and interesting.

**Reactions of Oxalic Acid.** Since oxalic acid has no alkyl chain it is not a typical acid of its series. Here again, as in many other cases, the first member of a homologous series differs from all of the others.

Oxalic acid is easily *oxidized* to carbon dioxide and water. This is readily accomplished with acidified potassium permanganate solution (standardization of potassium permanganate). It is more convenient to use potassium tetroxalate,  $\text{KHC}_2\text{O}_4 \cdot \text{H}_2\text{C}_2\text{O}_4 \cdot 2\text{H}_2\text{O}$ , as this is readily prepared in pure form and is very stable. *It may be used to standardize bases* as well as oxidizing

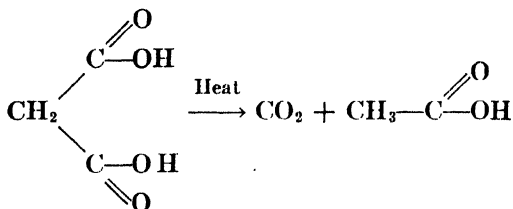
agents, one molecule of the salt being equivalent to three molecules of sodium hydroxide.

Ferric ion is reduced to ferrous. Thus potassium ferric oxalate when exposed to light is reduced to ferrous form. If then treated with platinous chloride, the platinum ion is reduced to the metallic form. These reactions form the basis for the use of potassium ferric oxalate for platinum prints in photography.

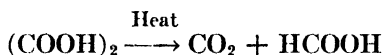
**Physiological Action.** Oxalic acid is an active poison. Strong solutions are caustic and corrosive like other acids, but dilute solutions are also toxic. This appears to be due to the insolubility of calcium oxalate. The precipitation of calcium oxalate upsets the body chemistry by withdrawal of necessary calcium ions. The higher acids of the series, whose calcium salts are more soluble in water, are far less toxic than oxalic acid.

#### EFFECT OF HEAT ON DICARBOXYLIC ACIDS

(1) *When two carboxyl groups are attached to the same carbon atom, carbon dioxide is lost.* Malonic acid, when heated, yields carbon dioxide and acetic acid:\*

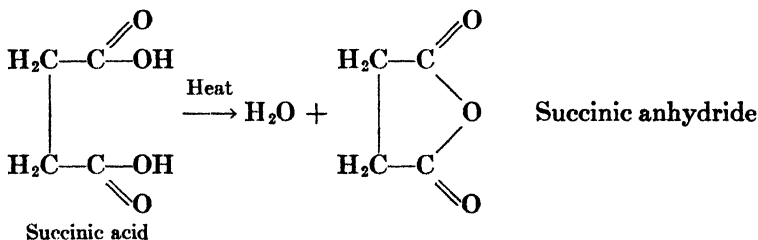


Oxalic acid under these conditions gives carbon dioxide and formic acid:



Oxalic anhydride cannot be made.

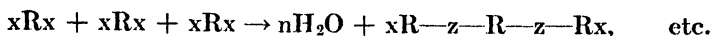
(2) *When the two carboxyl groups are joined to adjacent carbon atoms, water is lost coöperatively between the two hydroxyl groups.* This behavior recalls the reaction by which ethers are formed from alcohols (page 206).



(3) *When the carboxyl groups have more than three carbon atoms between them an intermolecular reaction occurs.* As explained in Chapter XXXII

\* It will be noted that the relationship between malonic and acetic acids is like that between oxalic and formic acids; in both pairs of acids either may be made directly from the other.

rings of less than five atoms do not form easily, and the same is true of rings with more than six or seven atoms. Succinic and glutaric acids easily form anhydrides. When we attempt to make an anhydride which would have a ring of seven or more atoms, we find it difficult or impossible to bring the molecule into the compact form required in the anhydride. Instead the carboxyl group of one molecule reacts with that of another molecule and we get a condensation polymer of high molecular weight:



It is possible that the ends of this large molecule may come together to form a very large ring, but this seems unlikely (see page 613).

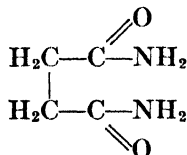
**Digression. Ester Formation from Dicarboxylic Acids with Dihydroxy Alcohols.** The esterification of a dicarboxylic acid with a dihydroxy alcohol presents interesting possibilities. It is evident that the esterification of malonic acid with ethylene glycol would produce a compound with a seven-atom ring, if the reaction proceeded simply. A ring of this size is not easily formed, therefore the molecules react with each other as indicated above under the discussion of anhydrides, producing a linear condensation polymer of high molecular weight:



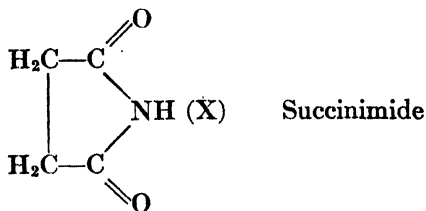
Compounds produced in this way from ethylene glycol and succinic or malonic acid, have molecular weights of about 2500-3500. Many such compounds find commercial uses because of their resin-like character (see page 505).

**Effect of Heat on Amides.** The normal amides of dicarboxylic acids lose ammonia when heated, forming ring compounds.

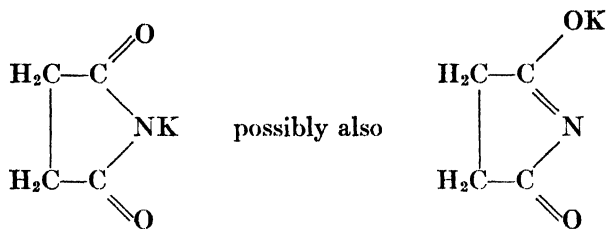
Thus succinamide,



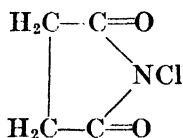
on being heated, liberates ammonia and yields the ring compound, succinimide:



The hydrogen of the imide marked (X), being *between two carbonyl groups*, is loosely held (acidic in nature). Succinimide, warmed with potassium hydroxide in alcohol solution, gives a potassium salt:



A synthetic use for such a salt is indicated in the Gabriel reaction, page 537. The acidic hydrogen is also replaceable by "positive" chlorine to form N-chlorosuccinimide:



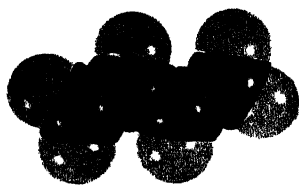
With water this compound hydrolyzes and gives hypochlorous acid. It has been proposed (patented) as a germicide for water. Reduction of succinimide gives the important aromatic compound pyrrole, page 642.

**Exchanges of Hydrogen for Deuterium.** A host of organic compounds in which hydrogen is partly or wholly substituted by deuterium has already been prepared. Many are made by treatment of a hydrogen compound with heavy water. Formic acid in this way exchanges H of the OH group for D, malonic acid exchanges all four hydrogens, but succinic only two (probably those of the carboxyl groups).

#### STRENGTH OF DICARBOXYLIC ACIDS

The following table showing the ionization constants of dicarboxylic acids is given for the benefit of comparison with the similar table for the monocarboxylic acids, to be found on page 170. In each case it is found that the first member of the series is by far the strongest, the percentage of ionization then decreasing very gradually after the third of the series. Oxalic acid is a much stronger acid than any one of the monocarboxylic acids.

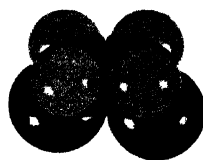
It is evident that the enhanced acidity of oxalic acid is due to the influence of one carboxyl group upon the other. This effect naturally diminishes when the two groups are more widely separated, as in malonic acid and other members of the series. We are familiar with the fact that



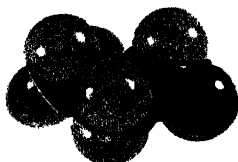
1,3-Butadiene



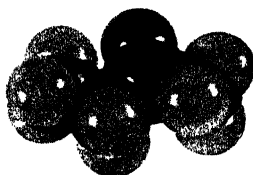
Propyne



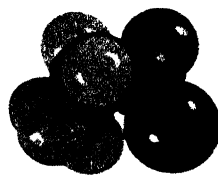
1,2-Dichloroethane



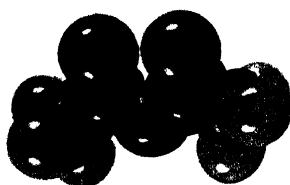
Propionaldehyde



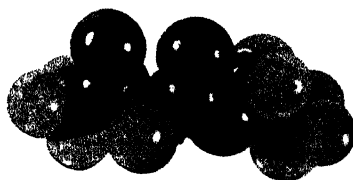
Ethyl methyl ketone



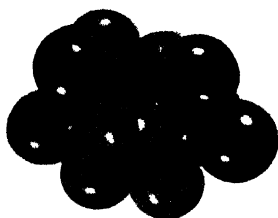
Propionyl chloride



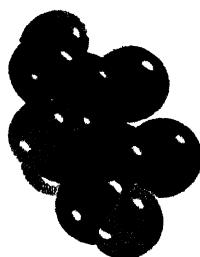
Acetic anhydride



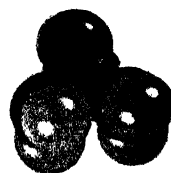
Ethyl acetoacetate



γ-Hydroxybutyric acid



Malonic acid



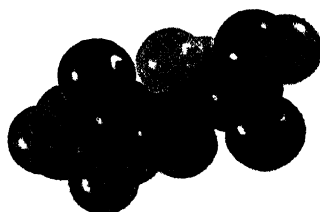
Urea



Acetonitrile



Ethylmethanamine



N-Glycylglycine



dicarboxylic acids ionize in stages. The ionization of one hydrogen from a dicarboxylic acid leaves a negative ion, which exerts an attractive force upon the remaining hydrogen. Hence the secondary ionization constant is never as great as the first. In the case of oxalic acid the second hydrogen is much more strongly held than with malonic acid, etc. (see table). No doubt this is due to the relatively small size of the oxalate ion.

TABLE 23.—IONIZATION CONSTANTS OF DICARBOXYLIC ACIDS

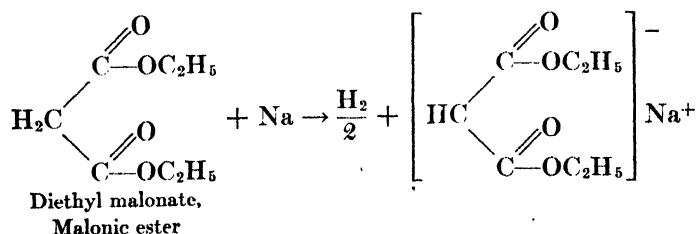
Name	T = 25°	K × 100	Ratio of first to second dissociation constant
Oxalic.....	(CO <sub>2</sub> H) <sub>2</sub>	3.8	1100
Malonic.....	CH <sub>2</sub> (CO <sub>2</sub> H) <sub>2</sub>	0.160	800
Succinic.....	(CH <sub>2</sub> ) <sub>2</sub> (CO <sub>2</sub> H) <sub>2</sub>	0.0066	25
Glutaric.....	(CH <sub>2</sub> ) <sub>3</sub> (CO <sub>2</sub> H) <sub>2</sub>	0.00475	16
Adipic.....	(CH <sub>2</sub> ) <sub>4</sub> (CO <sub>2</sub> H) <sub>2</sub>	0.0037	13
Pimelic.....	(CH <sub>2</sub> ) <sub>5</sub> (CO <sub>2</sub> H) <sub>2</sub>	0.00323	13

By the use of the table on page 172 an interesting comparison may be made between the "negativity" of the Cl atom and the carboxyl group when substituted for hydrogen of acetic acid. They are seen to have about the same effect upon the ionization.

## MALONIC ESTER SYNTHESIS

It has been shown (page 254) that malonic acid will yield acetic acid upon being heated. The reaction makes this compound very useful for the preparation of alkyl-substituted acetic acids, as well as for many other compounds. The manner of formation of these substituted acetic acids from diethyl malonate (malonic ester) is as follows:

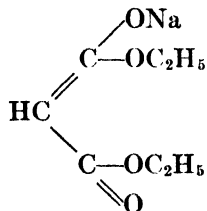
(1) The hydrogen of the CH<sub>2</sub> group of malonic acid derivatives (methylene hydrogen), like that in acetoacetic ester, is replaceable by sodium:



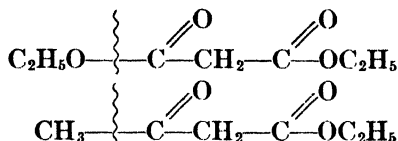
This replacement is possible because hydrogen on carbon next to a carbonyl group is not firmly fixed like that in a saturated hydrocarbon; this was



made apparent in our study of the aldehydes (page 149). When hydrogen is found on carbon *between two carbonyl groups*, it is so loosely held as to be easily replaced by metals. In other words compounds containing such "active" hydrogen behave in a measure like acids. We have seen this same behavior in the study of acetoacetic ester (page 208) which has an active methylene group, also in the salt-forming properties of succinimide (page 256). The sodium salt of malonic ester is possibly formed from an enol tautomer of the ester, as is the case with acetoacetic ester:

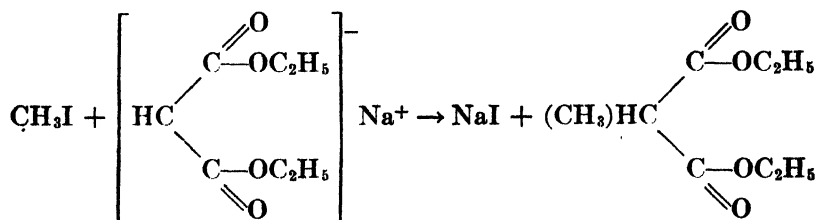


Attention is directed to the formulas of acetoacetic ester and malonic ester:

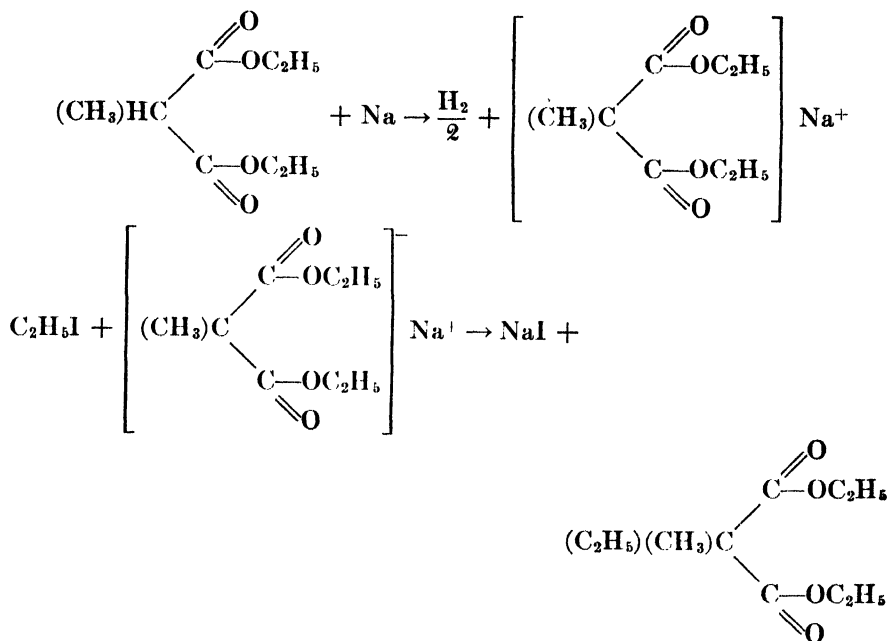


in which the similarity of structure of these two compounds is at once apparent.

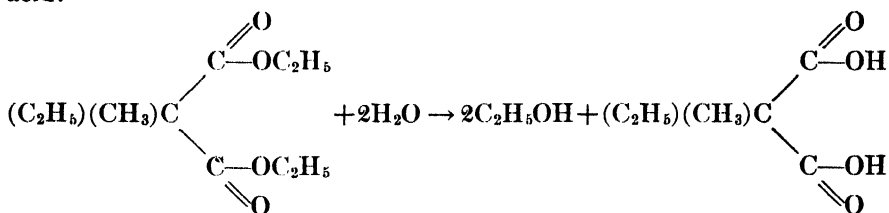
(2) The sodium compound obtained from malonic ester will react with an alkyl halide, resulting in the production of a derivative in which alkyl group takes the place of an original hydrogen of the methylene group.



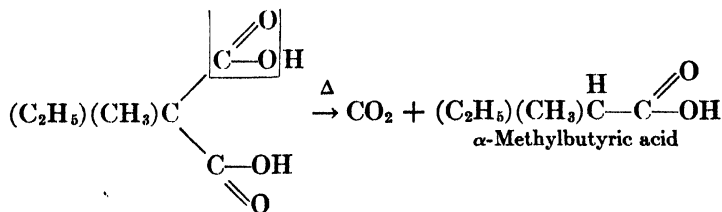
(3) The remaining hydrogen of the methylene group may now be replaced in like manner by an atom of sodium, and subsequently by another alkyl group, which may be the same as the first group introduced, or different from it:



(4) The hydrolysis of this compound would yield ethylmethylmalonic acid:



and the latter on being heated would lose carbon dioxide, to form ethylmethylacetic acid:



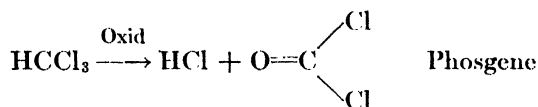
Various alkyl derivatives of acetic acid may be prepared by this method. The yields are usually better than in the acetoacetic ester synthesis, since in that method ketones as well as acids are formed. Dicarboxylic acids may be synthesized from malonic ester by methods somewhat similar to

those shown here. The use of malonic ester to make barbituric acid hypnotics is mentioned on page 274.

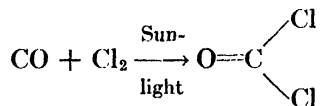
### CARBONIC ACID AND DERIVATIVES

Carbonic acid does not properly belong in the series of dicarboxylic acids; however it is convenient to consider this compound with them because of the similarity of its derivatives to those of the dicarboxylic acids. The pure acid has never been isolated; like other compounds having two hydroxyl groups joined to one carbon it is decomposed, yielding carbon dioxide and water. Its derivatives, however, show considerable stability and they play an important part in the field of organic chemistry. Among these derivatives are:

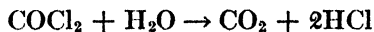
(1) *The Acid Chloride.* Carbonyl chloride,  $\text{COCl}_2$ , or phosgene, may be formed by the oxidation of chloroform:



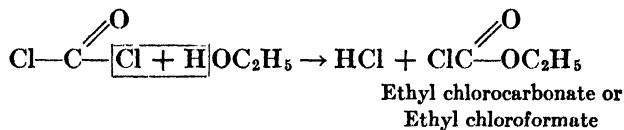
or by the union of carbon monoxide and chlorine:



Phosgene is a gas having a stifling odor, and is extremely poisonous. It was employed as a war gas, either alone or mixed with other substances which were poisonous or detrimental to comfort. Like other acid halides, phosgene is decomposed by water:

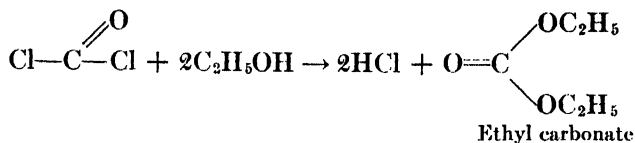


(2) *Esters.* (a) Chlorocarbonates. In its reaction with alcohols, phosgene is also a typical acyl halide. However the possession of two halogen atoms allows the formation of a new class of compounds, when only one of the halogens is brought into reaction:

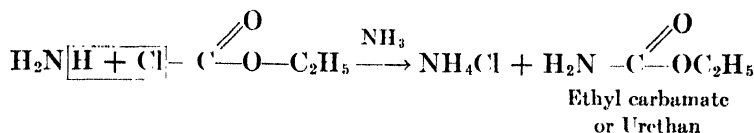


Substances formed by reaction of phosgene with one molecule of an alcohol are esters either of chloroformic acid or chlorocarbonic acid, and they are called by either name interchangeably. These compounds are both esters and acyl halides and are quite important in synthetic work.

(b) Normal esters. Normal esters of carbonic acid are formed by interaction of phosgene with two molecules of an alcohol:

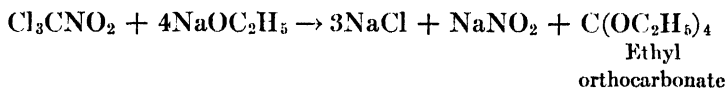


(c) Urethans. By the reactions of ammonia with chlorocarbonic esters the esters of carbamic acid (urethans) are formed:



Carbamic acid,  $\text{H}_2\text{NCOOH}$ , cannot be isolated as it breaks down into ammonia and carbon dioxide. The urethans have considerable importance in synthesis. Ethylurethan is used as a hypnotic (for animals) and sedative. It will be noticed that the urethans combine the structure of an ester and an amide.

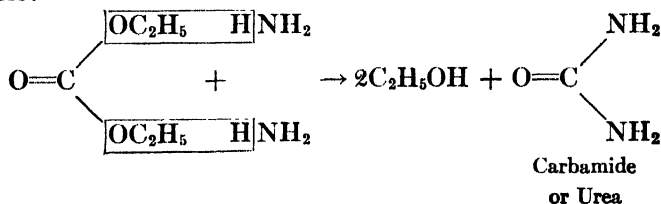
(d) Orthocarbonates. Orthocarbonates may be made as follows:



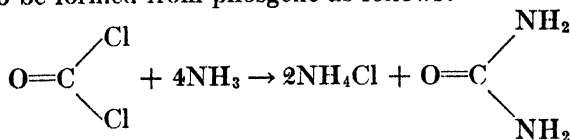
Orthocarbonates are esters of orthocarbonic acid,  $\text{C}(\text{OH})_4$ , which like carbonic acid is unstable, and has so far proved incapable of preparation.

(3) *Amides*. The esters of carbonic acid react like carboxylic esters (but more slowly) with ammonia; the amide is formed in the usual way (page 206).

Example:

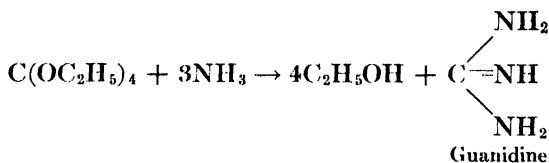


Urea may also be formed from phosgene as follows:



On account of the great importance of urea its reactions will receive separate treatment in the next chapter.

Ethyl orthocarbonate with ammonia gives guanidine:

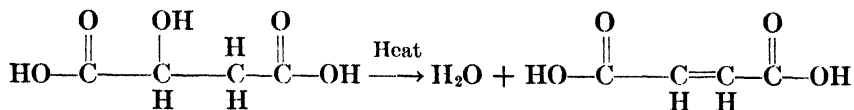


The chemistry of guanidine will be considered later along with the reactions of urea.

### UNSATURATED DICARBOXYLIC ACIDS

We have seen in the study of monocarboxylic acids that these compounds are derived from both saturated and unsaturated hydrocarbons. The same applies to the dicarboxylic acids, whose hydrocarbon group may be alkyl, alkylene, or acetylenic in type. The unsaturated acids derived from ethylene have industrial importance, and they interest the chemist because they display geometrical isomerism, a kind of isomerism common to ethylene derivatives (see page 59); the study of these acids has helped to explain the nature of space isomerism.

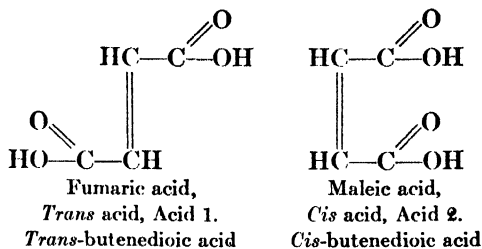
When malic acid (page 265) is submitted to dry distillation, its behavior is like that of other *beta*-hydroxy acids, i.e., water is lost and an unsaturated dicarboxylic acid results:



Along with this acid, which we shall call Acid 1, there is an acid anhydride of formula  $\text{C}_4\text{H}_2\text{O}_3$ . If this anhydride is treated with water, an acid is secured identical in *molecular formula* with Acid 1, but quite distinct from it in its properties. Briefly, the distillation of malic acid produces *two isomeric acids* of formula  $\text{C}_4\text{H}_4\text{O}_4$ . They are called maleic and fumaric acids.

One of these acids, Acid 1, has a melting point of  $287^\circ$ . It begins to sublime at about  $200^\circ$ . Its solubility in water is slight. When heated to a high temperature it forms an anhydride, but addition of water to the anhydride yields Acid 2.

Acid 2 melts at  $130.5^\circ$  and is quite soluble in water. If it is kept for some time at  $200^\circ$  it is converted into Acid 1; distilled with a dehydrating agent it forms an anhydride. Both acids are converted into succinic acid by reduction. The relationship between these two acids is best shown by the following formulas (see also page 328):

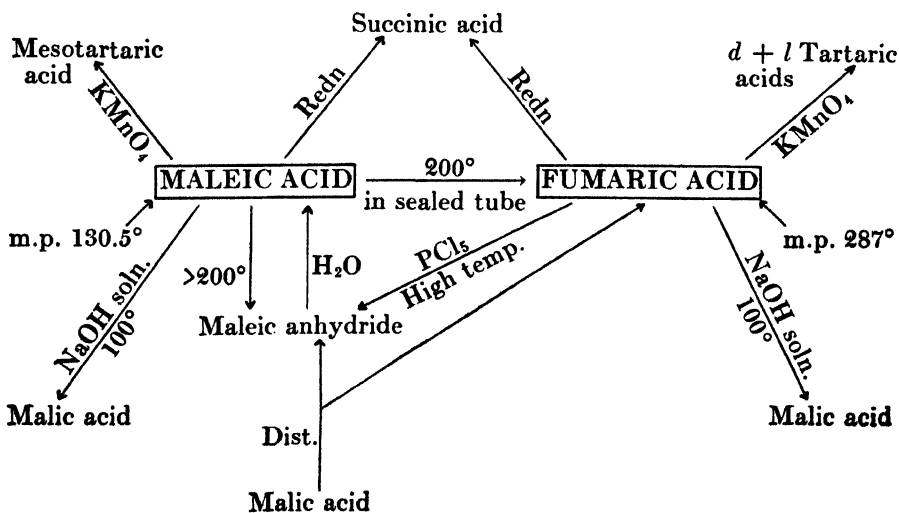


It has already been explained that when two carbon atoms are joined by a double bond, two permanently different arrangements of the molecule are possible (page 59). The structure having the two carboxyl groups near each other has been assigned to Acid 2, maleic acid, because it easily forms an anhydride, and such behavior is justified by a formula which shows the carboxyl groups in close proximity. A structure such as this in which the principal groups appear on the same side of the molecule is called a *cis* compound; the opposite type is called *trans*. Hence this kind of geometrical isomerism is also known as *cis-trans* isomerism. It is found in all types of compounds having a double bond (page 328).

TABLE 24.—MALEIC AND FUMARIC ACIDS

	Maleic	Fumaric
Configuration.....	<i>cis</i>	<i>trans</i>
M.p.....	130.5°	287°
B.p.....	135° dec.	290°
Solubility, H <sub>2</sub> O.....	good	low
Ratio of first to second dissociation constant.....	50,000	45

## SOME TRANSFORMATIONS OF MALEIC AND FUMARIC ACIDS

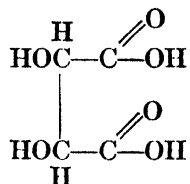


Commercially, maleic acid is prepared from benzene by air oxidation in the presence of a catalyst (page 409). The anhydride is produced in the same reaction. Both maleic and fumaric acids have industrial uses, however maleic anhydride has a greater number of applications. It is an important compound in connection with the Diels-Alder synthesis (page 618).

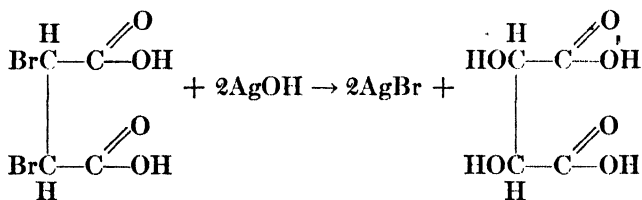
### POLYCARBOXYLIC HYDROXY ACIDS

Several of the more important of these compounds will be briefly described.

#### Tartaric acid,

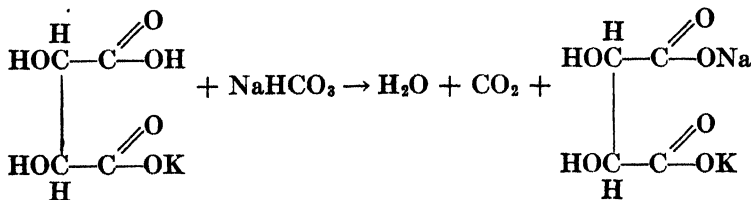


or dihydroxysuccinic acid, may be synthesized by the treatment of dibromosuccinic acid with moist silver oxide:



In nature the acid is found free, also in the form of salts of calcium or potassium. The commercial source of the acid is the potassium hydrogen salt, which occurs in fermenting grape juice as a deposit called *argol*.

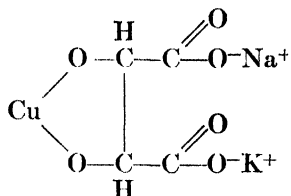
Pure potassium hydrogen tartrate, known as *cream of tartar*, is used in certain baking powders in which it is mixed with sodium bicarbonate. When water is added to this mixture, the free carboxyl group of the tartaric acid decomposes the bicarbonate:



The sodium potassium salt of tartaric acid is known as *Rochelle salt*. It is used for treatment of constipation (Seidlitz powders). In Fehling's solu-

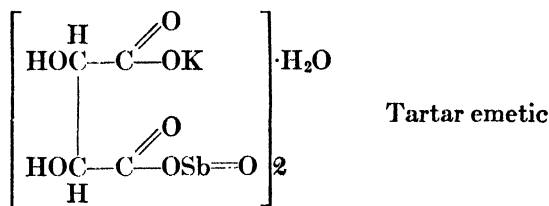
tion Rochelle salt is employed in a unique manner. This is an oxidizing solution containing copper sulfate; copper ion is the oxidizing agent. It is desirable to have the solution alkaline, as oxidation will proceed more readily in this medium; however the addition of alkali to copper sulfate would cause a precipitation of  $\text{Cu}(\text{OH})_2$  and remove practically all copper ion from the solution.

In the presence of Rochelle salt the following soluble salt is formed:

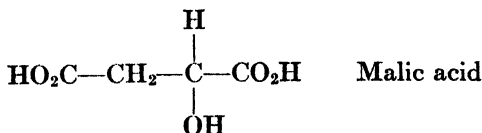


Copper hydroxide is not precipitated when alkali is added to this solution, and the copper ion is released as needed for the oxidation.

*Tartar emetic*, potassium antimonyl tartrate, is employed as an emetic and expectorant; also as a mordant in dyeing. In the chapter on optical activity we shall find that tartaric acid, like lactic acid, exists in several isomeric forms.



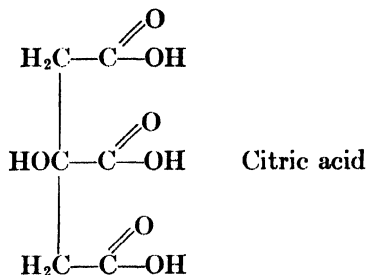
**Malic acid** may be made by partial reduction of tartaric acid, or better by adding water to maleic acid, which is obtained from benzene (page 409). It is monohydroxysuccinic acid. Malic acid is found in many plants, occurring in seeds, roots, stems, or leaves of various species, also in numerous fruits. The acid has medical and industrial uses.



**Citric acid**, like malic acid, is found in many acid fruits. It is easily obtained from lemon juice by neutralization with calcium carbonate, and



subsequent treatment of the calcium citrate with sulfuric acid; it is now being made by the fermentation of sugar solutions or molasses. Magnesium citrate is employed in medicine as a mild laxative.



Tributyl citrate is offered as a solvent and plasticizer for lacquers, varnishes, polishes, and as an antifoaming agent for dispersions in water. In making blueprint paper potassium ferricyanide is used with ferric ammonium citrate. In the parts of the paper which are exposed to light the ferric salt oxidizes citric acid and is reduced to the ferrous form. Upon washing the paper, ferrous ferricyanide is formed, while in those parts not light struck, the original unchanged salts are merely washed away. A blue image on white paper results.

#### IDENTIFICATION TESTS FOR TARTARIC ACID AND CITRIC ACID

**Tartaric Acid.** Calcium tartrate is precipitated upon addition of a solution of calcium chloride to a neutral solution of a tartrate. (The presence of ammonium salts will interfere with this precipitation.) The precipitate of calcium tartrate is soluble in sodium hydroxide solution; however, if this solution is heated the salt is again precipitated in a jelly-like form. Solutions of tartaric acid or tartrates will reduce ammoniacal silver nitrate solution giving a silver mirror.

Potassium hydrogen tartrate is sparingly soluble in cold water, while neutral potassium tartrate is quite soluble. Thus when potassium hydroxide solution is slowly added to a solution of tartaric acid, a precipitate appears after a time, but this again goes into solution as more potassium hydroxide is added.

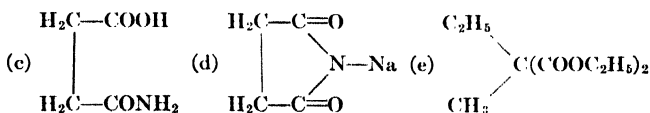
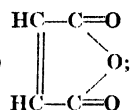
Dry tartaric acid or its salts decompose when heated giving an empyreumatic (burnt) odor, like burnt sugar; among other products we find pyruvic and pyrotartaric acids. Hot concentrated sulfuric acid also causes decomposition; the evolved gases smell of sulfur dioxide. Carbon monoxide and dioxide may also be detected.

**Citric Acid.** Tricalcium citrate is formed when a neutralized solution of citric acid is treated with calcium chloride. The salt is soluble in cold water, but is precipitated when its solution is heated. This calcium salt is not soluble in sodium hydroxide solution (note behavior of tartaric acid). The dry acid decomposes when heated, giving an irritating odor; carbon dioxide is one of the decomposition products. Hot concentrated sulfuric acid does not cause an immediate charring with citric acid as is the case with tartaric acid.

#### REVIEW QUESTIONS

1. Show by equations how oxalic acid may be made from: (a) HCN; (b) (CN)<sub>2</sub>; (c) from the elements.

2. Assign names to the following formulas. (a)  $\text{ClCOCH}_2\text{COCl}$ ; (b)



3. Write equations showing the formation of glutaric acid, also its reactions with: (a)  $\text{NH}_3$ ; (b)  $\text{EtOH}$ .
4. Show by equations the synthesis of malonic acid from acetic acid.
5. Write equations showing how the following compounds may be made by the malonic ester synthesis: (a) Dimethylacetic acid; (b) *n*-Butyric acid; (c) Propyl-methyl-acetic acid.
6. Write equations with graphic formulas for the following sequences.
- Diethyl malonate +  $\text{Na} \rightarrow (\text{A})$ ;
  - $(\text{A}) + \text{CH}_3\text{I} \rightarrow (\text{B})$ ;
  - $(\text{B}) + \text{Na} \rightarrow (\text{C})$ ;
  - $(\text{C}) + \text{C}_4\text{H}_9\text{I}(n) \rightarrow (\text{D})$ ;
  - $(\text{D}) + \text{hydrolysis, followed by heating of the resulting compound} \rightarrow (\text{E})$ .
7. Write sequences of equations with graphic formulas showing the preparation of the following compounds by means of the malonic ester synthesis. (a) Hexanoic acid; (b) Propanoic acid.
8. Write equations for three reactions of phosgene which are those of a typical acyl halide.
9. Outline the methods to be used to obtain carbon monoxide or carbon dioxide from oxalic acid.
10. Wherein does malonic acid differ chemically from succinic acid?
11. How might one pass from ethylene to succinic acid? from ethylene glycol to succinic acid?
12. Write a sequence of equations showing the preparation of succinic acid from *n*-propyl alcohol.
13. Explain the isomerism of maleic and fumaric acids.
14. Would ethylene glycol react with oxalic acid to form a monomolecular ester? Give reasoning to support your answer.
15. Write equations for the synthesis of diethyl malonate from sodium cyanoacetate.
16. Make a chart showing the chemical interrelations of maleic and fumaric acids.
17. When oxalic acid is sharply heated it does not char. How could you prove the presence of carbon in the compound?
18. Why would it be difficult to mistake a saturated monocarboxylic acid for a dicarboxylic acid?
19. Which derivatives of carbonic acid are similar in their chemistry to those of succinic acid, and which are dissimilar?
20. In what way is tautomerism different from other isomerism? Illustrate with specific examples.
21. It has been shown that alcohols may be made by the reduction of esters. Apply this method to the synthesis of 1,4-dihydroxybutane from the proper ester of the proper dicarboxylic acid.
22. What three carboxylic acids so far discussed in this book have unique chemical properties?
23. Make a chart of genetic relations for urea, indicating its connection with: phosgene, urethan, ethyl chlorocarbonate, ethyl carbonate.
24. What would be formed from the following reactions? (a) Succinic acid with phosphorus pentachloride (in excess); (b) Diethyl oxalate and alcoholic ammonia solution; (c) Phosphorus trichloride and monoethyl succinate.
25. Consider the melting point, density, boiling point, and solubility in water of the dicarboxylic acids. How should the numerical expression for each of these properties change

- as additional  $\text{CH}_2$  groups are placed between the carboxyl groups? Explain your predictions.
26. Write a series of balanced equations showing the synthesis of tartaric acid from glyoxal (ethanedial).
  27. Citric acid may be made from acetoacetic ester by the following series of changes. The reagents used are indicated in parentheses. Acetoacetic ester ( $\text{Cl}_2$ ) chloroacetoacetic ester ( $\text{KCN}$ ) cyanoacetoacetic ester (water, acid) acetonedicarboxylic ethyl ester (ethanol, catalyst) acetonedicarboxylic diethyl ester ( $\text{HCN}$ ) addition compound (water, acid) citric acid. Write a series of balanced equations for these reactions.
  28. There is a dicarboxylic acid, isomeric with succinic acid, known as isosuccinic acid. (a) Write its graphic formula; (b) Predict its behavior when heated; (c) Show its synthesis from *n*-propyl alcohol. NOTE. The hydrolysis of  $\text{CH}_3\text{CH}(\text{CN})_2$  gives succinic acid.
  29. How many cc. of 0.1N NaOH solution would be required for the neutralization of 1 g. of potassium tetroxalate?
  30. By the use of the following equation:
 
$$5 \text{ Oxalic acid} + 3 \text{H}_2\text{SO}_4 + 2 \text{KMnO}_4 \rightarrow 2 \text{MnSO}_4 + \text{K}_2\text{SO}_4 + 10 \text{CO}_2 + 8 \text{H}_2\text{O},$$
 predict the weight of potassium permanganate needed to oxidize 10 g. of oxalic acid.
  31. In which role is oxalic acid more effective (weight for weight), as a reducing agent or as an acid?
  32. A certain acid composed of C, H, and O contains 40.67% C, and 5.085% H. The molecular weight of its methyl ester is 146. When the ester is hydrolyzed and the free acid heated, carbon dioxide is lost and a new acid containing 48.66% C is produced. What is the structure of the original compound?

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## CHAPTER XIV

### UREA, THIOUREA, GUANIDINE, URIC ACID

The compound urea has been known to chemists since 1773, when it was discovered in urine (by Rouelle), where it normally occurs in a concentration of about 2%. The name urea suggests this source. From the physiological standpoint, urea has considerable importance, since it is the chief decomposition product resulting from the metabolism of nitrogenous material in the body. From 25 to 35 grams are voided daily by an average adult. Methods for the estimation of the urea content of the urine are of interest to the doctor.

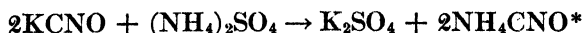
Historically, urea is a unique substance. Previous to its artificial synthesis by Wöhler in 1824, no organic compound had been made from inorganic or lifeless antecedents, and such a procedure was deemed impossible of accomplishment. The success of this synthesis overthrew the old conception of "vital force," giving fresh impetus to research in the field of organic chemistry.

Urea is a colorless crystalline compound, quite soluble in water and alcohol, but insoluble in ether. Its melting point is 132.7°. It has been obtained by evaporating urine and extracting the residue with hot alcohol, or better, by partial evaporation of urine and treatment with nitric acid. Urea is precipitated in the form of its nitrate, which after recrystallization is treated with barium carbonate. The mixture is then extracted with alcohol, whose evaporation yields the urea.

Urea is commonly called *carbamide*, a name which suggests that it is the di-*amide* of carb-*onic* acid. The syntheses which follow show that this is a correct conception. The monamide of carbonic acid is carbamic acid (see page 261).

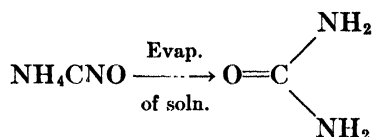
#### PREPARATION OF UREA

(1) The Wöhler synthesis. A water solution of potassium cyanate and ammonium sulfate on evaporation produces first ammonium cyanate:



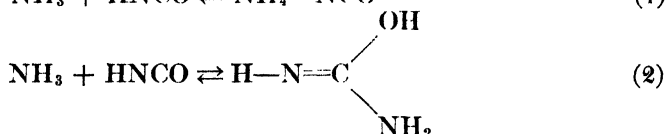
which on further evaporation rearranges itself to urea:

\* The original Wöhler synthesis was carried out with cyanogen and ammonia water and gave ammonium oxalate and other products in addition to urea. Subsequently the reaction was carried out in other ways.



The reaction is reversible, but at equilibrium the main product is urea.

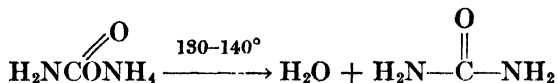
The equilibrium between urea and ammonium cyanate depends upon the fact that both yield ammonia upon dissociation. Ammonia may react with cyanic acid by (1) taking a proton in the customary way, thus forming a salt and (2) adding as H and NH<sub>2</sub> to the carbonyl group, giving urea (in its enol form). Note the equations below:



The removal of water suppresses reaction (1) which is completely reversed at high temperatures (ammonium salts dissociate when heated).

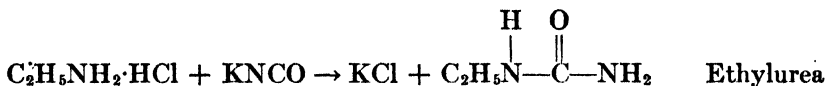
(2) General methods of amide formation suffice for the preparation of urea. The equations should be derived from those in the section on preparation of amides, page 227.

- (a) Formation from ester and ammonia; (for equation see pages 206, 261).
- (b) From the acid chloride and ammonia; (equation on pages 189, 261).
- (c) By heating the ammonium salt of carbamic acid:

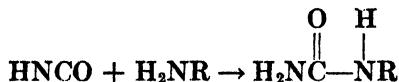


(d) **Commercial methods.** By the reaction of ammonia with carbon dioxide at 140° under pressure. (Ammonium carbamate (see equation c) is the first product of the reaction.) By the hydrolysis of cyanamide (page 295).

(3) The alkyl derivatives of urea are prepared by treating amines with cyanic acid:

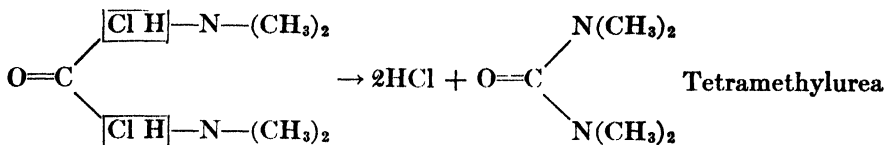


A more convenient and better method involves the evaporation of a solution in water or alcohol of an amine and nitrourea. The nitrourea dearranges into cyanic acid and nitroamide; the former then produces the substituted urea:



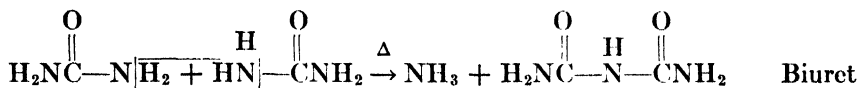
while the nitroamide decomposes to give nitrous oxide and water. The properties of monoalkyl ureas resemble those of urea.

Tetraalkyl derivatives of urea are prepared by treatment of secondary amines with phosgene:



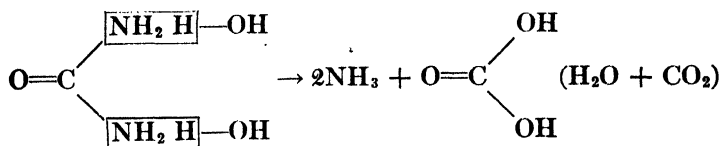
#### REACTIONS OF UREA

(1) *Action of heat.* Urea when heated above its melting point loses ammonia. A new compound called biuret is produced:



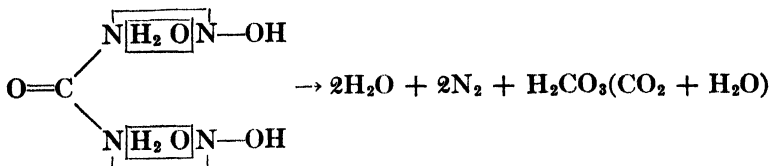
An alkaline solution of biuret gives with copper ion a violet color (the "biuret test"). The above procedure serves as a test for urea in the absence of proteins and certain other substances, which because of their possession of a "biuret grouping" also give the test. (See page 723.) Ordinarily the heating of urea also produces cyanic acid and ammonia; the cyanic acid then undergoes polymerization to cyanuric acid and other substances.

(2) *Hydrolysis.* Urea, like any amide, hydrolyzes to yield its acid and ammonia:



Hydrolysis is expedited by the use of a base or an acid; it is promoted as well by the enzyme *urease*, which is present in castor- or jack bean. Certain organisms present in the soil also cause hydrolysis of urea, ammonium carbonate being formed thereby.

(3) *Reaction of nitrous acid.* Monamides, as we have seen, react with nitrous acid, liberating nitrogen gas and forming their acids (page 228). Urea also reacts in this manner:



In performing a nitration urea may be added to remove nitrous acid. This

removal is beneficial because nitrous acid is a catalyst for the oxidizing action of nitric acid.

(4) *Reaction of alkaline hypobromite solution* (Hofmann, 1881). Urea is oxidized when treated with a solution of potassium or sodium hypobromite.

The gaseous products are nitrogen and carbon dioxide, the latter being absorbed by the excess base present:

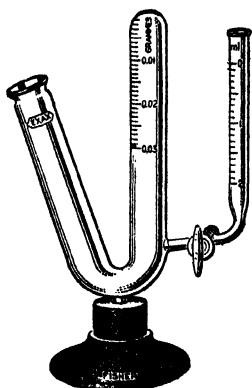
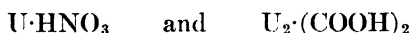


FIG. 33.—Doremus-Hinds ureometer for determination of urea in urine.

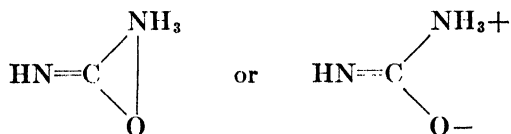
Urine may be treated in a ureometer (Fig. 33) with alkaline hypobromite solution to determine the amount of urea it contains (by noting the volume of nitrogen released), but the method is not strictly accurate. The more modern procedure is to decompose the urea by the use of a solution of urease, and measure the amount of ammonia which results by means of titration with standard acid.

(5) *Action of mineral acids; salt formation.*

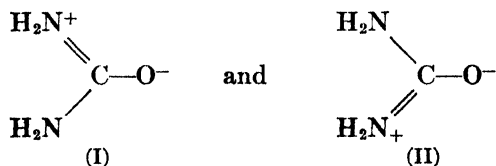
Urea forms salts with acids. The nitrate and oxalate crystallize well from nitric acid and alcohol respectively. Letting the symbol U stand for urea the formulas of these salts are:



The symmetrical formula for urea would, however, predict the formation of  $\text{U} \cdot (\text{HNO}_3)_2$  and  $\text{U} \cdot (\text{COOH})_2$ . The fact that these salts do not form gives support to the unsymmetrical Werner formula for urea which is:



There is other experimental evidence in favor of the Werner formula, but it has not survived the test of time. Present opinion is that urea is a resonance hybrid and that its structure can best be visualized as lying between the two structures shown herewith.

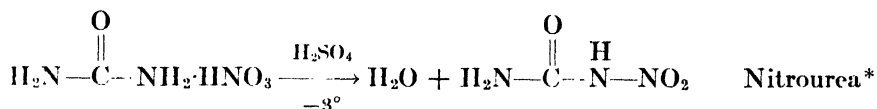


**Resonance.** In the case of many organic molecules it is possible to construct two or more graphic formulas which differ from each other only

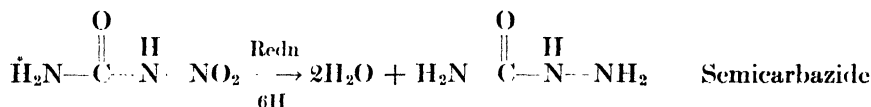
in the disposition of certain valence electrons. The methods of wave mechanics have shown that in such cases the molecules adapt themselves by assuming a structure intermediate between the limiting states shown in the formulas. The molecule is said to be a resonance hybrid of the two or more possible structures.

Urea, for example, is considered to be a resonance hybrid of structures (I) and (II), p. 272. The actual structure lies between these and partakes of the nature of both of them. As a consequence the true structure of urea or of any other resonating molecule cannot be shown by a single graphic formula. See page 398 for further discussion.

Urea nitrate is useful for the preparation of *nitrourea*:

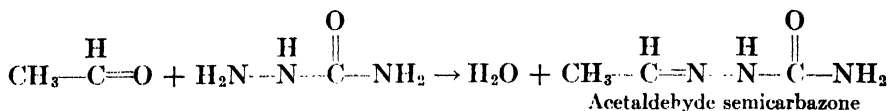


The nitrourea is reduced electrolytically to produce the important reagent aminourea or *semicarbazide*:

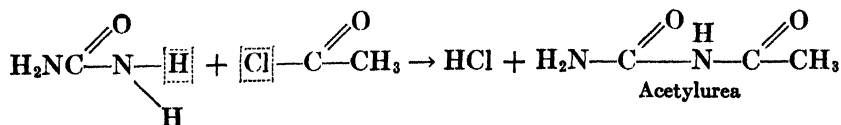


Semicarbazide is used with aldehydes and ketones in much the same way as phenylhydrazine. The reaction is of the same type, and usually furnishes a crystalline derivative which is suitable for purposes of identification. The products are called semicarbazones.

Example:



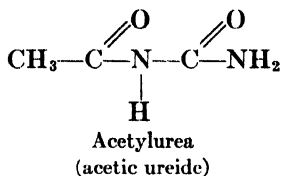
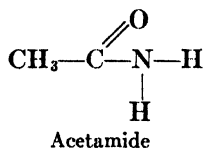
(6) *Action of organic acids* (acid halides, acid anhydrides):



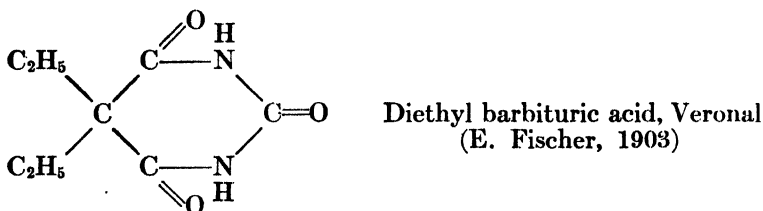
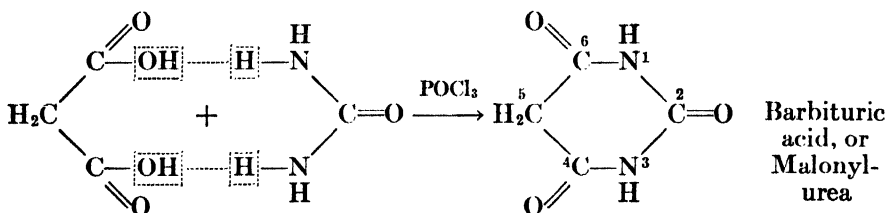
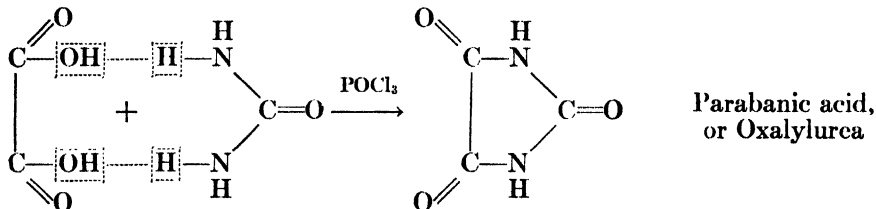
Compounds called *ureides* are formed. These are analogous to amides in method of formation, and in structure.

\* Both urea nitrate and nitrourea are powerful explosives.

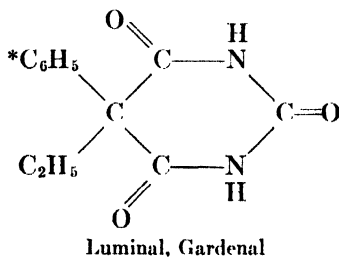




(7) *Reaction of dicarboxylic acids.* The dicarboxylic acids by their action with urea form ureides which are cyclic compounds. The formulas of a few of these compounds follow:



For one method of introducing the ethyl groups, see reactions of malonic ester, Chapter XIII.



Another method of forming veronal is to condense diethyl malonic ester with urea with the help of sodium ethoxide. Many hundreds of compounds of the type of veronal have been made, to be used as hypnotics, anesthetics,

\* See page 396.

and preanesthetic sedatives. The names of some of these with the groups corresponding, are:

Name	Groups (in 5,5 position)
Allonal.....	Isopropyl, allyl (with pyramidon)
Amytal.....	Ethyl, isoamyl
Nembutal.....	Ethyl, 2-secondary amyl

These compounds are only sparingly soluble in water, but form sodium salts which are quite water-soluble and are used in medical practice. In spite of the large number of such compounds already made there is very active research in the synthesis of additional members. The compounds have these advantages; they work quickly and can be given either by mouth or by injection. They are not habit forming. On the debit side are the digestive and other disturbances which frequently follow their use. Research is directed mainly to trial of new substituting groups and to variation of positions of substituting groups in the molecule.

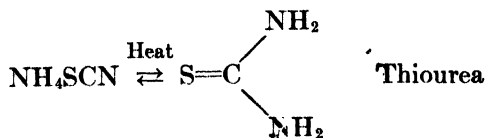
Within the past few years a number of thiobarbiturates, made with thiourea instead of urea, have been tried as hypnotics. Several have shown promise of success. They acted very promptly and allowed quick recovery after sleep. One such is Pentothal, the sulfur analog of Nembutal.

#### USES OF UREA

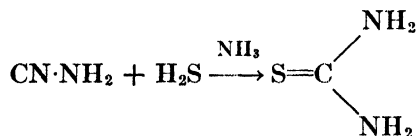
Large amounts of urea are used in compounding fertilizer. Its high nitrogen content and ease of hydrolysis make it a good substance through which to restore nitrogen to the soil. Since urea reacts with nitric acid, it is used as a stabilizer for nitrocellulose products (explosives) in which nitric acid or its oxides might accumulate as a result of decomposition. Vast amounts of urea are used to form resins, for example with formaldehyde. About 1500 tons of urea were so used in 1935. It is claimed that a 2% solution of urea has great value in relieving pain and promoting healing in skin infections, burns, carbuncles, and slow healing wounds in general. Urea is used in many other ways, e.g., for making varnishes, dyes, pyroxylin, etc. A recent use is as basic material for the synthesis of sulfamic acid,  $\text{H}_2\text{NSO}_3\text{H}$ , whose ammonium salt is a valuable flameproofing material for fabrics and paper. Urea is now used to prevent splitting and checking of lumber during the drying or seasoning process, also to treat wood which is to be bent and shaped.

#### THIOUREA

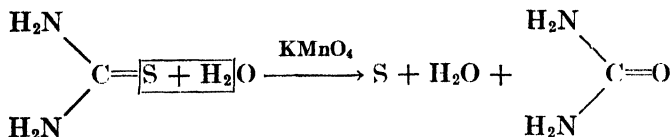
The sulfur analog of urea, thiourea, may be prepared by a method similar to the Wöhler synthesis of urea, from ammonium thiocyanate:



It may also be made from hydrogen sulfide and cyanamide in the presence of ammonia:



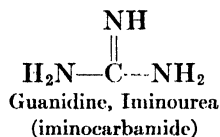
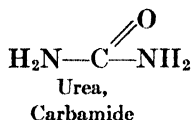
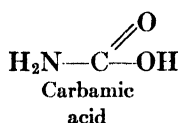
Thiourea reverts to urea when treated with cold permanganate solution:



Neither thiourea nor its alkyl derivatives are worth an extended discussion. The aromatic derivatives of thiourea are, however, of importance (page 468).

### GUANIDINE (Strecker, 1861)

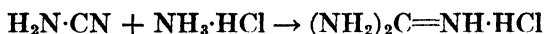
This compound is closely related to urea and may be thought of as the amidine\* of carbamic acid, urea being its amide.



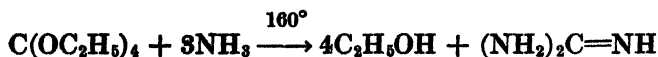
Guanidine is found in beet juice; its derivatives creatine and creatinine are products of protein metabolism, and the latter is constantly present in the urine in small amounts.

Guanidine is a colorless, crystalline, hygroscopic solid, soluble in water and alcohol. It is a more basic compound than urea, due to the presence of three ammonia residues. Guanidine absorbs carbon dioxide from the air, forming its carbonate, and unites with one equivalent of acids to yield stable salts. The nitrate is sparingly soluble in water.

**Preparation.** (1) Guanidine may be prepared from cyanamide and ammonium chloride. When these are heated in alcohol solution the hydrochloride of guanidine is obtained:



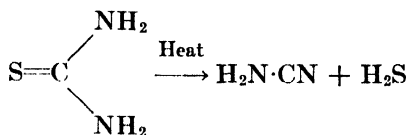
(2) Another method involves the reaction of an ester of orthocarbonic acid and ammonia:



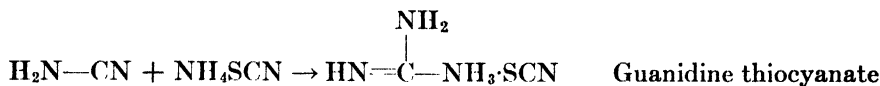
(3) Ammonium thiocyanate, when heated, produces guanidine. The action of heat on ammonium thiocyanate rearranges this substance to

\* =NH is the imino (imido) group; in an amidine it is substituted for oxygen of an amide.

thiourea as has been shown. This then breaks down to  $\text{H}_2\text{S}$  and cyanamide:

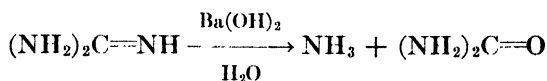


By action of ammonium thiocyanate upon cyanamide, guanidine thiocyanate is formed:



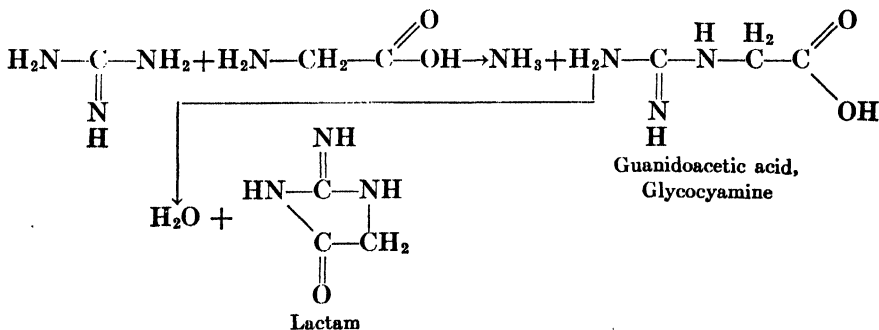
#### REACTIONS OF GUANIDINE

(1) *Guanidine treated with barium hydroxide solution yields urea:*



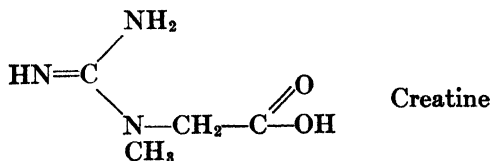
(2) *Derivatives with acids.* Guanidine, like urea, forms derivatives with acids. Guanidine nitrate and nitroguanidine, easily made from it, are used as explosives. Several of the derivatives which are of physiological importance are illustrated below.

(a) *With glycine.* Guanidoacetic acid is formed by loss of ammonia and then passes to its lactam by loss of water:

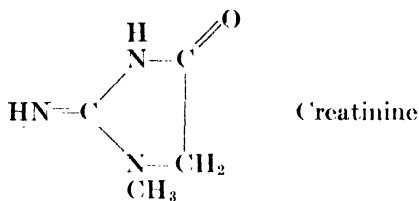


(b) *Other derivatives.*

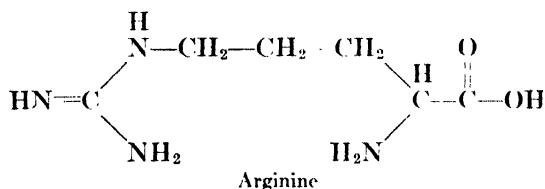
**Creatine.** N-methylguanidoacetic acid. This compound is found in the fluids of muscles. Its anhydride is creatinine.



**Creatinine.** Found in extract of beef and in human urine.



**Arginine**,  $\alpha$ -amino- $\delta$ -guanidovaleric acid, a derivative of guanidine, is one of the decomposition products of the proteins (page 716).

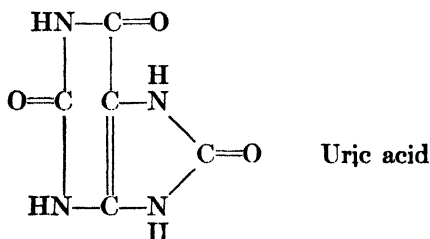


### URIC ACID

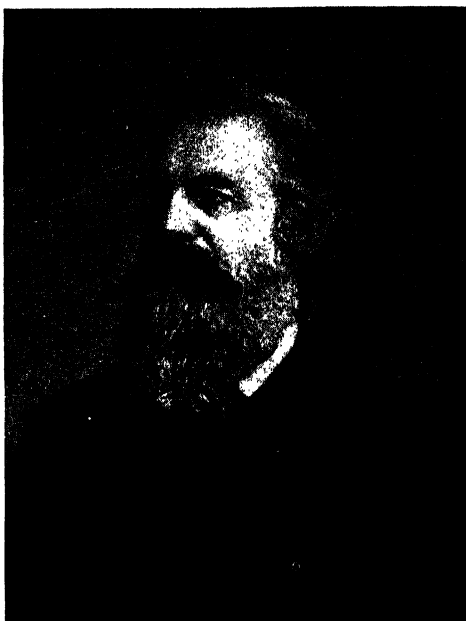
Uric acid occurs in small amounts in the urine, from which it was first isolated by Scheele in 1776. With man, this compound represents but an insignificant part of the total nitrogen eliminated, while with birds and reptiles it is the chief constituent of the excreta. It may be prepared from guano, which is the excrement of certain sea birds, or from snake excrement, either of which sources contains the ammonium salt.

In gout or in arthritis there may be an overproduction of uric acid by the body. This forms deposits of sodium urate in the joints; often urinary calculi or stones are composed of uric acid or urates.

Uric acid is very sparingly soluble in water and insoluble in alcohol and ether. There are no carboxyl groups in the compound; however it acts like a weak dicarboxylic acid, forming two series of salts. The chemistry of uric acid is in many respects too difficult for an elementary presentation; on the other hand, several steps in its synthesis follow naturally from what has already been set forth, and the physiological importance of this compound also demands at least a brief consideration.



JOHANNES A. WISLICENUS. (1835-1902, German.) Outstanding research chemist, best known for the acetoacetic ester and malonic ester syntheses, for the synthetic production of lactic acid. He noted the difference between *d*- and *l*-lactic acids and foretold (1869) that this difference would have to do with the space arrangement of the atoms. See *J. Chem. Soc. (London)*, **87**, 501 (1905); also this book, page 332.

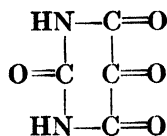


*Berichte*, **37**, 4861 (1904).



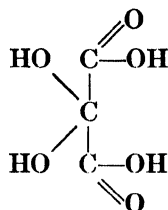
FRIEDRICH K. BEILSTEIN. (1838-1906, Russian.) Compiler of the monumental "Handbook" of organic chemistry which today comprises over fifty volumes. Beilstein discovered the isomerism of benzyl chloride and chlorotoluene. See *J. Chem. Soc. (London)*, **99**, 1646 (1911), *J. Chem. Education*, **15**, 51, 303, 310 (1938); also this book, page 9.

**Structure.** Uric acid has a structure which suggests its possible formation from urea after the manner in which cyclic ureides are prepared. In fact, the oxidation of uric acid with  $\text{HNO}_3$  yields alloxan:



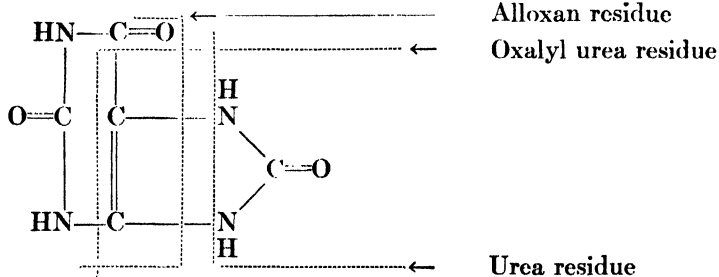
the ureide of mesoxalic acid,

Alloxan



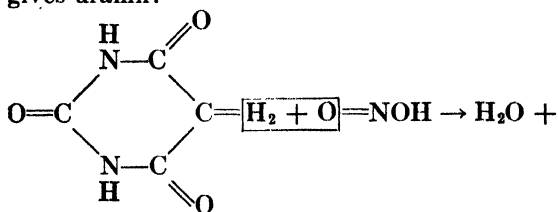
Mesoxalic acid

also parabanic acid, or oxalyl urea, and urea. The dotted lines across the uric acid formula show the position of these fragments in the complete structure:

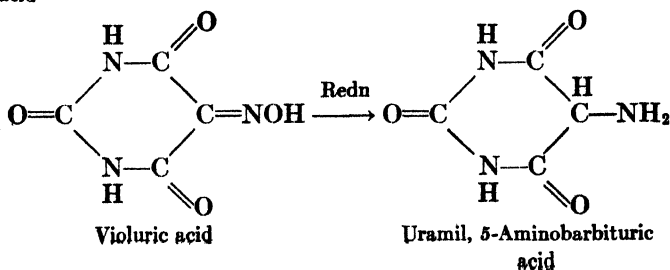


#### SYNTHESIS OF URIC ACID (Baeyer and E. Fischer)

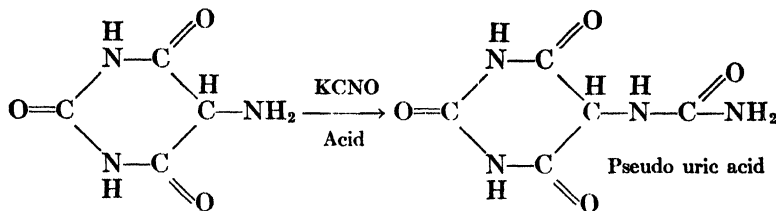
Barbituric acid with nitrous acid yields violuric acid, which on reduction gives uramil:



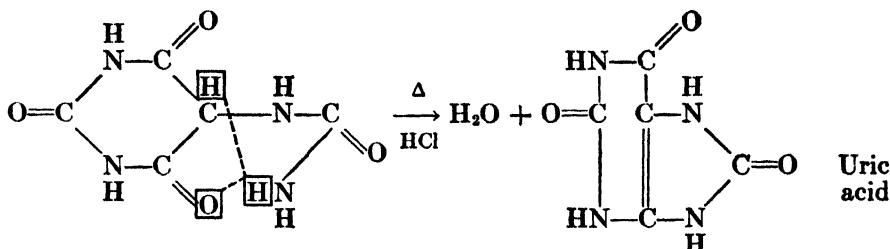
Barbituric acid



Pseudo uric acid is formed from uramil:

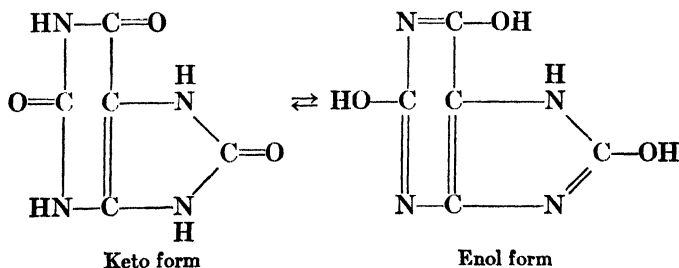


The dehydration of pseudo uric acid gives uric acid:



Johnson has recently announced the isolation from tea leaves of 1,3,7,9-tetramethyluric acid, first synthesized by Emil Fischer in 1884. This is the first reported instance of the occurrence of a methyl derivative of uric acid in nature. A yield of about 10 g. was secured from several million pounds of tea.

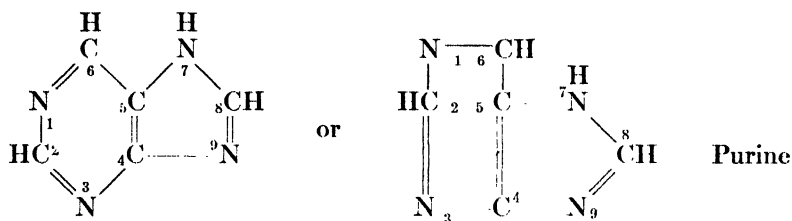
Uric acid in some of its reactions behaves as if it had three hydroxyl groups, again as if it were a ketone. We must therefore suppose that the compound exhibits keto-enol tautomerism. The formation of salts by a compound which has no carboxyl groups is also explained by this assumption (see acetoacetic ester, malonic ester, succinimide).



All of the oxygen derivatives of purine (see below and page 648) show keto-enol tautomerism as does uric acid.

It is convenient to consider both uric acid and its derivatives as if derived from the synthetic C, H, N compound, Purine, as they all contain this structure as a nucleus. By numbering the corners of the purine structure as shown, the various derivatives are easily described (see page 648).





The rectangular formulas used up to this point emphasize the relationship of uric acid to urea. The second formula given for purine adheres to this scheme. Formulas of this type are still used by many chemists. However, it is also desirable to consider these compounds and others related to them along with the heterocyclic compounds, and for this reason the purine and pyrimidine compounds will be found in Chapter XXXIV.

### REVIEW QUESTIONS

- How may urea be prepared: (a) from urine? (b) synthetically? (Give three methods.)
- Estimate the volume of nitrogen which would be liberated from 0.25 g. of urea by treatment with alkaline hypobromite solution; (b) by treatment with nitrous acid.
- A sample containing urea was treated with alkaline hypobromite solution. The sample weighed 0.25 gram and liberated 55.98 cc. of nitrogen. Calculate the percentage of urea in the sample.
- A sample of pure urea when hydrolyzed neutralized 45.0 cc. of N/10  $\text{H}_2\text{SO}_4$  solution. What was the weight of the sample?
- Write equations for the action of urea with nitrous acid; with propionyl chloride.
- Cite several reactions which justify the name "carbamide" for urea.
- What is a ureide? Show formation of a cyclic ureide.
- Show how urea may be synthesized from: (a) Thiourea; (b) Guanidine.
- Indicate the reactions by which you would prepare veronal.
- What compound might be formed from the reaction of ethyl carbonate and urea?
- How can you explain the fact that mesoxalic acid has two hydroxyl groups on one carbon atom?
- Write the formula for the purine derivative recently found in tea by Johnson (page 281). How do you account for the fact that this compound was synthesized in 1884 and only found in nature after a lapse of 53 years?
- Show by the use of graphic formulas the different tautomeric forms possible for creatinine.
- What differences are observed when dry acetamide and dry urea are heated?
- A water solution of cyanogen after standing some hours is found to contain ammonium oxalate and urea. Explain, with equations, how these compounds are formed.
- When making ethyl nitrate from ethyl alcohol and nitric acid, urea is added to avoid formation of ethyl nitrite. Explain, with equations.
- Explain the formation of guanidine from cyanamide and ammonium chloride.
- A water solution of urea (A) has a specific gravity equal to 1.00. A 5 cc. sample of this solution when treated with sodium hypobromite solution liberates 38 cc. of nitrogen. What is the percentage concentration of urea in solution (A)?
- When urea is heated above its melting point, cyanic acid and ammonia are produced. Explain the formation of biuret from these products and unchanged urea.
- List the substances mentioned in this chapter which (a) are anesthetics; (b) are used in the detection and estimation of urea; (c) contain sulfur; (d) may be used to synthesize urea.

21. Write graphic formulas for the following hypnotics, derivatives of barbituric acid: Neonal (5-ethyl-5-*n*-butyl compound); Dial (5,5-diallyl compound).
22. Assign names to the following formulas.
- (a)  $\text{HNCO}$ ; (b)  $\text{H}_2\text{NCO}_2\text{NH}_2$ ; (c)  $\text{C}_3\text{H}_7\text{NHCONH}_2$ ; (d)  $\text{O}=\text{C}(\text{OH})_2$ ; (e)  $\text{H}_2\text{NCONH-NH}_2$ ; (f)  $\text{HN}=\text{C}(\text{NH}_2)\text{N}(\text{CH}_3)\text{CH}_2\text{CO}_2\text{H}$ .
23. Name four important organic compounds which may be made from carbon monoxide. Write complete equations for the synthesis of these compounds.
24. Write equations for reactions of four different organic compounds which yield carbon dioxide (or a carbonate) as a by-product.

#### LITERATURE REFERENCES

1. KRASE, GADDY and CLARK. A direct synthetic urea process. *Ind. Eng. Chem.*, **22**, 289 (1930).
2. WARREN. Wöhler's synthesis of urea. *J. Chem. Education*, **5**, 1539 (1928).
3. VOLWILER and TABERN. 5,5-Substituted barbituric acids. *J. Am. Chem. Soc.*, **52**, 1676 (1930).
4. TABERN and SHELBERG. Physico-chemical properties and hypnotic action of substituted barbituric acids. *J. Am. Chem. Soc.*, **55**, 328 (1933).
5. SHONLE. Hypnotic action and chemical structure. *Ind. Eng. Chem.*, **23**, 1104 (1931).
6. KUMLER and FOHLEN. The dipole moment and structure of urea and thiourea. *J. Am. Chem. Soc.*, **64**, 1944 (1942).
7. CUPERY. Sulfamic acid. *Ind. Eng. Chem.*, **30**, 627 (1938).

## CHAPTER XV

# NITRILES, ISONITRILES, AND RELATED COMPOUNDS; NITRO COMPOUNDS

## NITRILES OR ALKYL CYANIDES

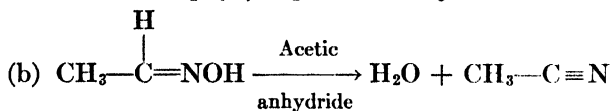
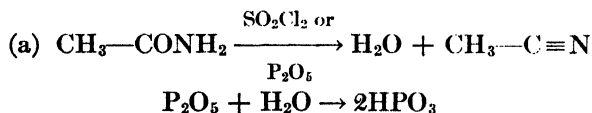
The nitriles are colorless liquids (up to  $C_{14}$ ) or solids. The first few members of the series are slightly water-soluble and have peculiar but not unpleasant odors. They are C, H, N compounds, of type  $R-C\equiv N$ .

They may be formed from:

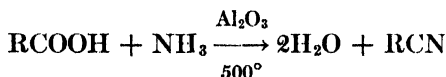
(1) A primary or secondary alkyl halide and potassium cyanide, by double decomposition:



or by the dehydration of (a) amides or (b) aldoximes:



(2) A nitrile is produced when the vapor of an acid is passed with ammonia over a catalyst heated to about  $500^\circ C$ .



**This is the commercial method of production.**

The first synthesis is a means of adding carbon atom to a chain. In (a) and (b) the previous history of the starting compound proves the structure of the nitrile; we know that the methyl group is joined to carbon and not to nitrogen. These syntheses differ from the first in that they do not yield isocyanide.

## NOMENCLATURE

These substances are called *nitriles* and are named from the acids formed by their hydrolysis, or from the parent hydrocarbon, with the addition of "nitrile."

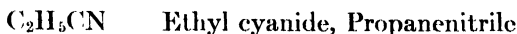
\* There is a small yield of  $CH_3NC$ .

Example:



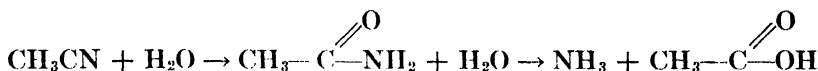
Also they are called *alkyl cyanides*.

Example:



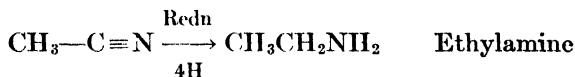
#### REACTIONS OF NITRILES

(1) *Hydrolysis*. Formation of amide or fatty acid. Partial hydrolysis of a nitrile yields an amide; complete hydrolysis gives the corresponding acid; i.e., its ammonium salt.



The hydrolysis is expedited by the use of either base or acid. If carried out with alkaline hydrogen peroxide it may be halted at the amide stage.

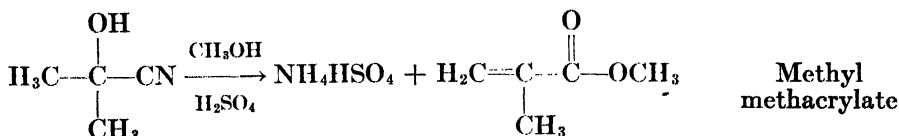
(2) *Reduction*. Formation of a primary amine. When carried out with sodium in absolute alcohol this is known as the Mendius reaction (1862).



This reaction confirms the fact that in a nitrile the carbon of the CN group and carbon of the alkyl group are directly attached.

(3) *Reactions with alcohol*. (a) Formation of an imido-ester (imido group in place of oxygen of an ordinary ester). The formula for such an ester is given on page 230. The hydrochloride of the imido ester is formed by reaction with the alcohol in the presence of dry hydrogen chloride.

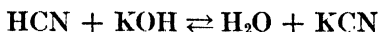
(b) A nitrile reacts with an alcohol in the presence of sulfuric acid to give an ester:



The polymerization of methyl methacrylate gives the resin called Lucite (page 505).

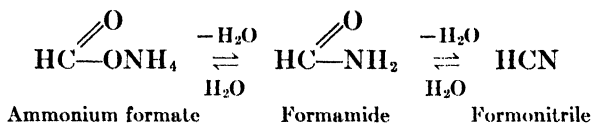
**Formonitrile.** It has been stated before that the first member of a homologous series may have anomalous reactions, besides possessing all of the typical reactions of its class. This is clearly seen in the case of formonitrile (HCN), the first of the series of cyanides. The presence of the cyanide group imparts such activity to the hydrogen that this substance acts like an acid; hydrogen is replaced by active metals, also salts are

formed with bases. These facts receive recognition when we call this compound "hydrocyanic acid" (prussic acid). It is a very weak acid, much weaker than carbonic acid.



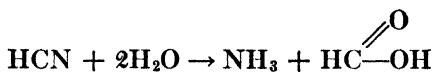
Hydrogen cyanide is an extremely poisonous, low-boiling, colorless liquid, soluble in water. It may be obtained from the glucoside amygdalin by hydrolysis. The typical reactions of cyanides are shown below for hydrogen cyanide.

*Formation:*

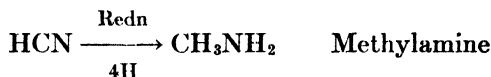


The commercial preparation is from the action of sulfuric acid upon an alkali cyanide.

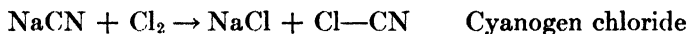
*Hydrolysis:*



*Reduction:*



The hydrogen of HCN may be replaced by halogen, like hydrogen of an alkyl group. Compounds like cyanogen chloride, bromide, etc., are secured in this way.

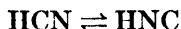


*Cyanogen chloride* is a gas; the corresponding bromide and iodide are solids. All have very irritating, tear provoking vapor, and are actively poisonous (see page 323). They are valuable in synthesis. Inspection of the formula of cyanogen chloride shows that it is the acid chloride of cyanic acid.

*Cyanamide* may be formed from the chloride by action of ammonia:

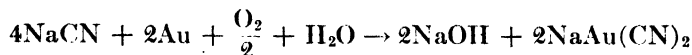


Hydrogen cyanide is known to be a tautomeric compound existing in two forms:



It exists almost entirely in the HCN form and the equations shown above are for that form. The HNC form is represented in various derivatives; for example the isocyanides shown in the next section.

**Uses of HCN.** Chief uses of hydrogen cyanide depend upon its high toxicity. It is used as a fumigant for fruit trees, in ships, as a lethal gas in some states for the execution of criminals. The use of potassium cyanide in silver plating depends upon the formation of the complex salt  $\text{KAg}(\text{CN})_2$  from excess of  $\text{KCN}$  and  $\text{AgCN}$ . The complex salt ionizes but slightly, hence when used in electroplating an even coating results. If the solution were highly charged with silver ions the plating would tend to be uneven, perhaps spongy. The same principle is applied to gold plating. In the "cyanide process" for the extraction of gold, a soluble cyanide is used in the presence of oxygen (air). The gold dissolves as a complex salt:

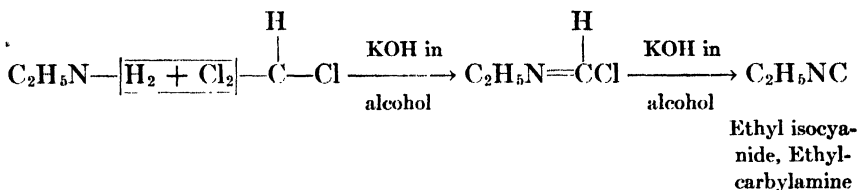


#### ISOCYANIDES, ISONITRILES, OR CARBYLAMINES

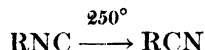
When an alkyl halide is treated with *silver cyanide* an isonitrile is formed:



The Hofmann reaction (page 311) used to identify primary amines, also produces isocyanides:



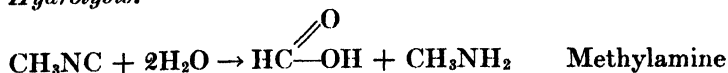
Isocyanides are colorless liquids with very disagreeable odors. They are poisonous substances. They are water-insoluble compounds whose boiling points lie 20 to 30° below the boiling points of the corresponding nitriles. When heated to 250° rearrangement to cyanide takes place:



Evidently the  $\text{RCN}$  arrangement is more stable than  $\text{RNC}$ , as  $\text{HCN}$  is more stable than  $\text{HNC}$ .

#### REACTIONS

(1) *Hydrolysis:*

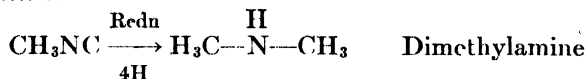


The isonitrile hydrolyzes to yield a primary amine, while the nitriles by hydrolysis give the corresponding fatty acids. It is plainly seen that in an isonitrile the nitrogen of the  $\text{CN}$  group attaches to carbon of the alkyl

\* This is the principal product; there is also some  $\text{CH}_3\text{CN}$ .

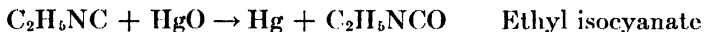
group. The acid hydrolysis of isonitriles is far more rapid than the corresponding hydrolysis of nitriles. Isonitriles are stable toward alkali.

(2) *Reduction:*

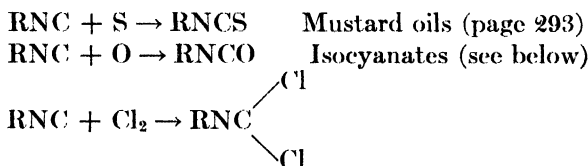


Note that a primary amine can be formed from either nitrile or isonitrile (by different methods). On reduction nitriles yield primary amines, whereas secondary amines are formed from the isonitriles in this way.

(3) *Oxidation:* The oxidation of an isocyanide gives an isocyanate:



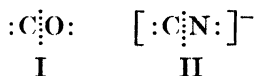
(4) The isocyanides readily react *by addition* with a number of substances:



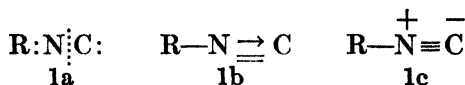
**Structure.** Since the added atoms have been proved to join with the carbon of the isonitrile, the following formula,  $\text{RN}=\text{C}$ , having *divalent\** carbon has been used for these compounds and is still in favor with many organic chemists. The addition reactions of carbon monoxide, analogous to the above reactions (note equation for formation of phosgene, page 260) have similarly given support to the formula  $\text{C}=\text{O}$ .

These formulas have been satisfactory to chemists, since they rationalize quite well the unusual reactions of the compounds. Unfortunately they must be abandoned, as the modern methods of physics and chemistry, when applied to the isocyanides, do not uphold a formula with divalent carbon.

The modern formulas for carbon monoxide and for cyanide ion are as shown below:



Each is characterized by the sharing of six electrons between the atoms and by the possession of "lone pairs." The cyanide ion is seen to have the same structure whether furnished by a cyanide or an isocyanide. If hydrogen or an alkyl group shares the lone pair of the carbon, we have a cyanide; if the lone pair of the nitrogen is shared, we have an isocyanide.



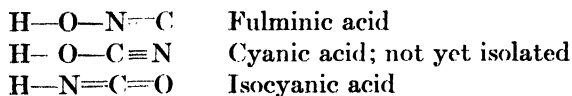
\* See footnote, page 15.

In an alkyl isocyanide the activity of the carbon atom is due to its possession of a lone pair (1a); in the cyanide, nitrogen is active for the same reason. The arrow in formula (1b) and the plus and minus signs in (1c) have the same meaning. They indicate that one of the valences is "coördinate"; that is, that two of the electrons in the octet for carbon came from the nitrogen; carbon is the "acceptor." In an ordinary covalent link each atom contributes *one* electron, but in a coördinate link one atom has a share in *two* electrons from another atom (see page 127).

**Difference in Behavior of Potassium Cyanide and Silver Cyanide.** It was noted that the reaction of an alkyl halide with potassium cyanide gives mainly an organic cyanide, while its reaction with silver cyanide gives mainly an isocyanide. One attempt to explain this calls attention to the fact that potassium cyanide is an ionic compound. If an alkyl halide reacts with potassium cyanide, the reaction is probably with the ion. Either RNC or RCN could result, but the latter is the more stable arrangement. Silver cyanide is very little ionized and may be considered as a molecular compound ( $\text{Ag}:\text{C}::\text{N}:$ ). The reaction of an alkyl halide with this molecule is influenced by the lone pair of the nitrogen, which causes the alkyl carbon to unite there. Thus the RNC structure results. There are weak points in this explanation which has been presented very briefly. More facts are needed from research before this problem can be thoroughly understood.

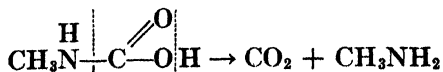
#### ISOCYANATES

The oxidation of potassium cyanide, KCN, leads to the formation of potassium cyanate, KOCN, a derivative of cyanic acid. This acid exists in several isomeric forms:



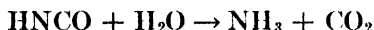
Inorganic cyanates and fulminates are well known; however, well defined organic derivatives have not yet been made. On the other hand the organic isocyanates are well recognized substances. They may be formed as suggested before by the oxidation of isonitriles. They are intermediate substances in the reaction of hypobromites with amides (Hofmann reaction, page 306), and hydrolyze to yield amines and carbon dioxide in the last step of this reaction.

Probably a substituted carbamic acid is first formed, which, like carbamic acid itself, is unstable:





Cyanic acid may be obtained from its salts in the customary way. In the presence of a strong acid decomposition ensues:

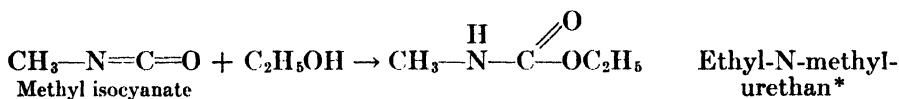


Pure cyanic acid may be made by heating cyanuric acid, ( $\text{C}_3\text{H}_3\text{N}_3\text{O}_3$ ). It must be kept below  $0^\circ$  to avoid change. It is a volatile strong acid smelling like acetic acid. On standing cyanic acid passes to tripolymers known as cyamelide and cyanuric acid.

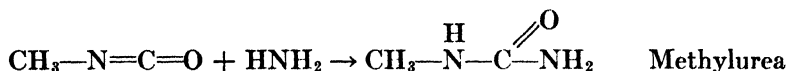
Alkyl isocyanates (but not cyanates) are made by reaction of alkyl halides with silver cyanate or alkyl sulfates with potassium cyanate, or by oxidation of carbylamines as has been shown. Isocyanates are liquids with a disagreeable odor.

### REACTIONS

(1) *With alcohols, isocyanates yield urethans:*

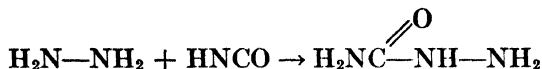


(2) *With ammonia, substituted ureas are produced:*



In both cases the reaction is one of addition.

(3) *Hydrazine reacts readily with cyanic acid to give semicarbazide* (see page 273):

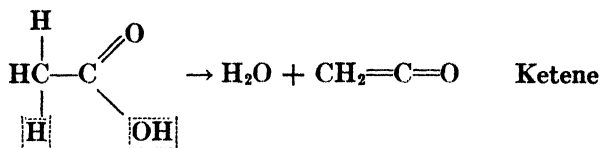


The formation of urea from ammonium cyanate has already been noted (page 270). The reaction resembles that with hydrazine.

Phenyl and  $\alpha$ -naphthyl isocyanates are used to identify alcohols and amines, with which they form ureas and urethans as indicated here.

### KETENES

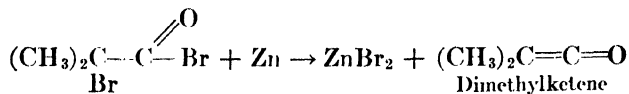
Ketenes are highly reactive compounds, which are derived from acids in the same sense that olefins are derived from alcohols, i.e., by loss of H and OH from adjacent carbon atoms:



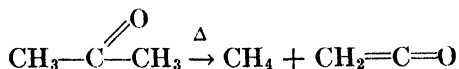
\* See footnote, page 306.

While ketene may be made directly from acetic acid by heating it to 500°, other methods of preparation are better.

**Preparation.** Some ketenes may be prepared from  $\alpha$ -halogen acyl halides by the action of zinc:

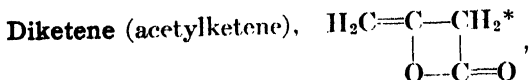
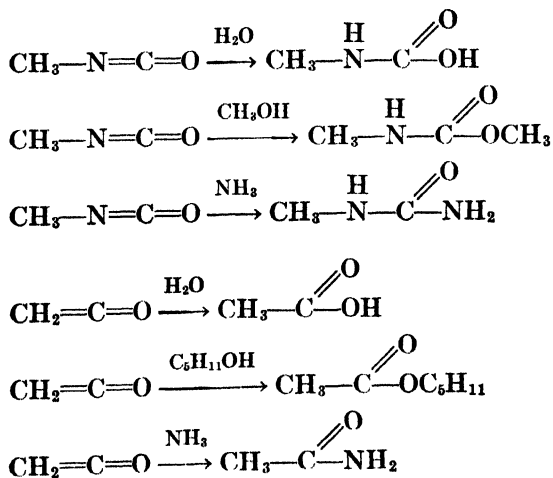


Ketene itself is formed in reasonable yield when acetone is passed through a heated tube:



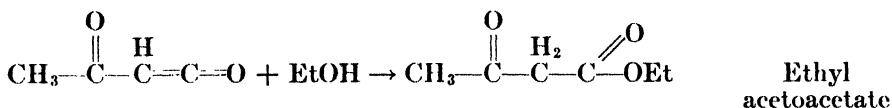
The Ketenes are divided into aldoketenes,  $\text{RCHC}=\text{O}$ , and ketoketenes,  $\text{R}_2\text{C}=\text{C}=\text{O}$ . Ketene itself is a poisonous, colorless gas. Aldoketenes are in general colorless liquids of unpleasant odor. The ketoketenes are colored yellow or red. Due to the great unsaturation of these compounds they display an unusual activity. Aliphatic representatives, especially aldoketenes, polymerize with extreme ease. Oxygen (air), water, alcohols, amines, acids, halogens, Grignard reagents, etc., enter into reaction with the ketenes.

**Reactions.** In their reactions the ketenes resemble the isocyanates. This forms the basis for inserting this material here. This likeness will be seen by inspection of the comparative reactions indicated in the following equations:



\* The structure of diketene is still uncertain. See *J. Am. Chem. Soc.*, **65**, 1677 (1943).

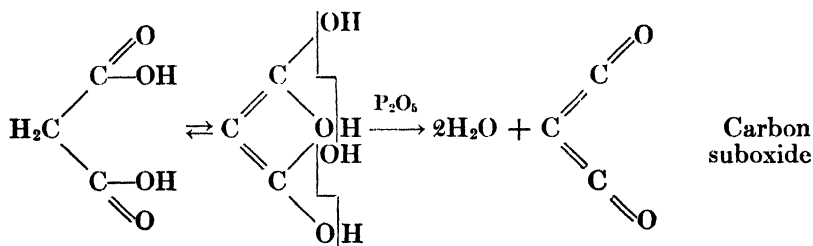
a dimer of ketene formed by polymerization, is of interest, since its reaction with an alcohol gives an ester of acetoacetic acid. This is a commercial method of preparation.



The important compound acetoacetanilide is formed by addition of aniline. This will be discussed later in connection with Hansa dyes.

**Carbon Suboxide**,  $\text{C}_3\text{O}_2$ , obtained when malonic acid is dehydrated with phosphorus pentoxide, is a typical ketene. This is a poisonous, colorless gas, which easily polymerizes to a solid. The substance shows great chemical activity as would be expected in view of its unusual structure.

#### Preparation.



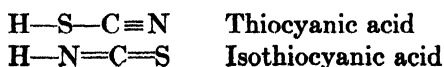
#### FULMINIC ACID

Fulminic acid,  $\text{HONC}$ , has interest in connection with the history and development of organic chemistry. Silver fulminate was prepared and analyzed in 1823 by Liebig, who found that it gave the same analytical data as silver cyanate. After a short period of indecision the fact was accepted that two different compounds can have the same molecular formula, and the name *isomerism* was coined by Berzelius to apply to such cases.

Today interest in fulminic acid centers in the mercury salt, which is highly explosive and is used as a detonator in cartridges and in large guns. It can be fired either by shock or by heat. It is made from action of nitric acid and ethyl alcohol on mercury, as when first made in 1800. Free fulminic acid is a very poisonous gas (?) which quickly polymerizes. It smells like  $\text{HCN}$ .

#### THIOCYANATES AND ISOTHIOCYANATES

Thiocyanic acid and its inorganic salts are well known. This acid, like cyanic, exists in several isomeric forms:

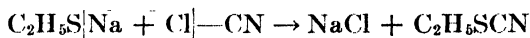


Inorganic thiocyanates are obtained from cyanides by addition of sulfur as cyanates are produced by addition of oxygen. The salts of HNCS are not known but organic derivatives can be made.

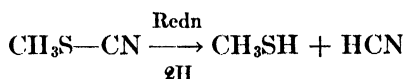
Thiocyanic acid, made from the potassium salt by the action of sulfuric acid, is a gas which very quickly polymerizes, forming a yellow solid. The organic thiocyanates have the type formula  $R-S-C\equiv N$ . These are oily liquids with a somewhat garlic-like smell. They may be prepared by a method like that used to obtain the alkyl cyanides:



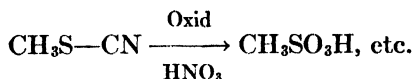
or they may be prepared by the action of a mercaptide upon a cyanogen halide:



This synthesis forms a proof of the structure of thiocyanates. Thiocyanates on reduction yield thioalcohols and hydrogen cyanide:

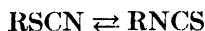


Their oxidation gives sulfonic acids:



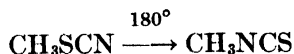
This reaction gives a second proof of structure.

When thiocyanates are brought to a high temperature they rearrange to isothiocyanates:

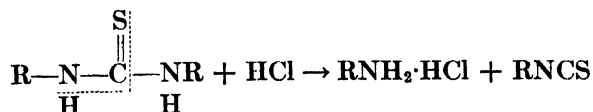


**Isothiocyanates.** These have the type formula RNCS and are called *mustard oils* because the allyl compound,  $C_3H_5-NCS$ , is contained in mustard seed. The well known odor and taste of mustard are due to this compound. Other plants contain mustard oils.

**Preparation.** (1) By rearrangement of the corresponding thiocyanate, induced by heat:

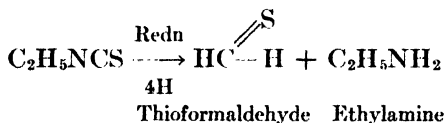


(2) From disubstituted thioureas by the action of an acid:



It is interesting to note that while the reduction of a thiocyanate yields a

thioalcohol, the reduction of the isomeric isothiocyanate leads to the formation of an amine:



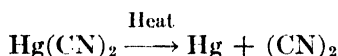
In each case these products would have been predicted from the structures presented for these compounds, i.e., the reasoning which established their structures rests upon these and similar reactions.

Mustard oils react with alcohols and amines as indicated for the isocyanates. They yield *thiourethans* and *thioureas* in this way.

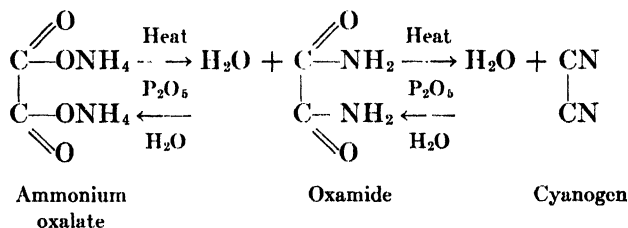
### CYANOGEN

The organic compounds considered in this section (cyanides, isocyanides, etc.) are derivatives of cyanogen  $(\text{CN})_2$ ,\* which merits momentary consideration for this reason. Cyanogen is a colorless gas, soluble in water and quite poisonous, with a pungent odor. It burns in air with a violet flame.

**Preparation.** (1) It may be prepared by heating mercuric cyanide:

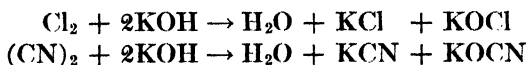


(2) It is also made by heating ammonium oxalate, or by dehydration with  $\text{P}_2\text{O}_5$ .



This reaction is reversible. The relation of cyanogen to oxamide and ammonium oxalate is the same as that between any organic nitrile, amide, and ammonium salt. (See page 286.)

**Reactions.** With alkalis cyanogen reacts as would a halogen:



The derivation of cyanates and cyanides from cyanogen is shown in this equation.

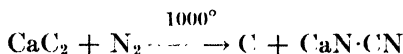
\* They may also be considered as derivatives of  $\text{HCN}$ .

## DERIVATIVES OF CYANOGEN

**Cyanogen chloride** (see page 286).

**Cyanamide**,  $\text{H}_2\text{N}-\text{CN}$ , has the structure of carbamic acid nitrile. It is a white hygroscopic solid, soluble in water, alcohol, and ether. Its formation from cyanogen chloride and ammonia is shown on page 286.

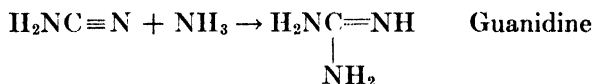
Its calcium salt may be made from calcium carbide by heating in nitrogen gas in presence of lime:



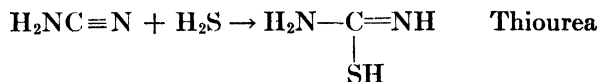
Both hydrogens of the amino group are replaceable by metal; the CN group like  $\text{C}=\text{O}$  renders hydrogen on adjoining nitrogen or carbon acidic.

Addition reactions of cyanamide are typified in the following examples.

(1) *Addition of ammonia:*

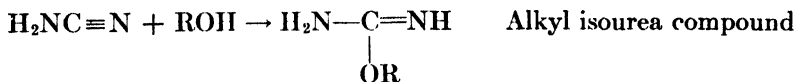


(2) *Addition of hydrogen sulfide:*

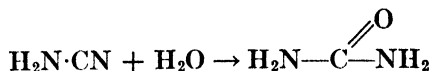


Treatment of thiourea with mercuric oxide yields cyanamide. This is a good method of preparation.

(3) *Addition of alcohol:*

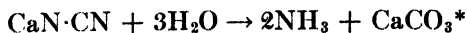


(4) *The hydrolysis of cyanamide yields urea:*



and finally carbonic acid and ammonia, if hydrolysis is continued.

*Calcium cyanamide by its hydrolysis gives ammonia and calcium carbonate:*



Calcium cyanamide is used as a fertilizer ("Nitrolime"), giving both ammonia and lime to the soil. Since it can be made from atmospheric nitrogen (see equation above) we have here a means of transferring nitrogen from the air to the soil and thence to growing plants.

\* In the soil, calcium cyanamide decomposes in other ways than shown here, liberating cyanamide (which hydrolyses to urea) and other products.

TABLE 25.—DATA FOR HYDROGEN CYANIDE AND DERIVATIVES

Name	Properties	Inorganic salts	Organic compounds	Hydrolysis yields:	Reduction yields:
Hydrogen Cyanide, HCN	Weak acid, $K = 13 \times 10^{-10}$ M.p., $-14^{\circ}$ B.p., $26^{\circ}$ Tautomeric. Poisonous.	Known	Nitriles, isonitriles	Formic acid	Methylamine
Fulminic acid, HONC	Not known free. Poisonous, odor of HCN.	Known	Unknown	Formic acid, hydroxylamine	
Cyanic acid, HOCN	Strong acid, unstable, polymerizes.	Known	Unknown	Ammonia, carbon dioxide	
Isocyanic acid, HNCO			Isocyanates	Ammonia, carbon dioxide	
Thiocyanic acid, HSCN	Gas, stable only below $0^{\circ}$ . Strong acid.	Known	Thiocyanates		Thioalcohol, HCN
Isothiocyanic acid, HNCS	Tautomeric		Mustard oils		Thioformaldehyde, amine

TABLE 26.—CYANIDES AND RELATED COMPOUNDS

Names	Formula	M.p., $^{\circ}\text{C}$ .	B.p., $^{\circ}\text{C}$ .	Sp. g.
Hydrogen cyanide.....	HCN	$-14$	$26$	$0.697^{18^{\circ}}$
Methyl cyanide, Acetonitrile.....	$\text{CH}_3\text{CN}$	$-41$	$81.6$	$0.789^{20^{\circ}/4^{\circ}}$
Ethyl cyanide, Propanenitrile.....	$\text{C}_2\text{H}_5\text{CN}$	$-91.9$	$97.1$	$0.783^{11^{\circ}/4^{\circ}}$
Methyl isocyanide, Methylcarbylamine....	$\text{CH}_3\text{NC}$	$-45$	$59.6$	$0.756^{4^{\circ}}$
Ethyl isocyanide, Ethylcarbylamine.....	$\text{C}_2\text{H}_5\text{NC}$	$< -66$	$78-9$	$0.744^{25^{\circ}}$
Methyl isocyanate.....	$\text{CH}_3\text{NCO}$	.....	$43-5$	
Ethyl isocyanate.....	$\text{C}_2\text{H}_5\text{NCO}$	.....	$60$	$0.898$
Methyl thiocyanate.....	$\text{CH}_3\text{SCN}$	$-51$	$130-3$	$1.069^{24^{\circ}/4^{\circ}}$
Ethyl thiocyanate.....	$\text{C}_2\text{H}_5\text{SCN}$	$-85.5$	$145^{765}\text{ mm.}$	$0.996^{26^{\circ}/4^{\circ}}$
Methyl isothiocyanate, Methyl mustard oil	$\text{CH}_3\text{NCS}$	$35-6$	$119^{759}\text{ mm.}$	$1.069^{37^{\circ}/4^{\circ}}$
Ethyl isothiocyanate, Ethyl mustard oil...	$\text{C}_2\text{H}_5\text{NCS}$	$-5.9$	$131-2$	$1.004^{15^{\circ}/4^{\circ}}$
Cyanogen.....	$\text{C}_2\text{N}_2$	$-34.4$	$-20.5$	$0.866^{-17^{\circ}}$
Cyanogen chloride.....	CNCl	$-6.5$	$12.5-13$	$1.222^{0^{\circ}}$
Cyanogen bromide.....	CNBr	$52$	$61.3^{750}\text{ mm.}$	$2.015^{20^{\circ}/4^{\circ}}$
Cyanamide.....	CNNH <sub>2</sub>	$44-5$	$140^{19}\text{ mm.}$	$1.073^{48^{\circ}/4^{\circ}}$

## NITRO COMPOUNDS

As was shown on page 199 the reaction of silver nitrite with an alkyl halide gives a nitro compound. A methyl halide gives a good yield of nitromethane; with halides of larger radicals the yield of alkyl nitrite is considerable. A more practical method for the preparation of nitroparaffins is the momentary treatment of paraffins with nitric acid at temperatures near 400°C. At this high reaction temperature both nitration and pyrolysis take place; the exact course of the reaction is not known with certainty (see Reference 9, page 300). The ease of replacement of hydrogen by nitro group is in the order: tertiary > secondary > primary.

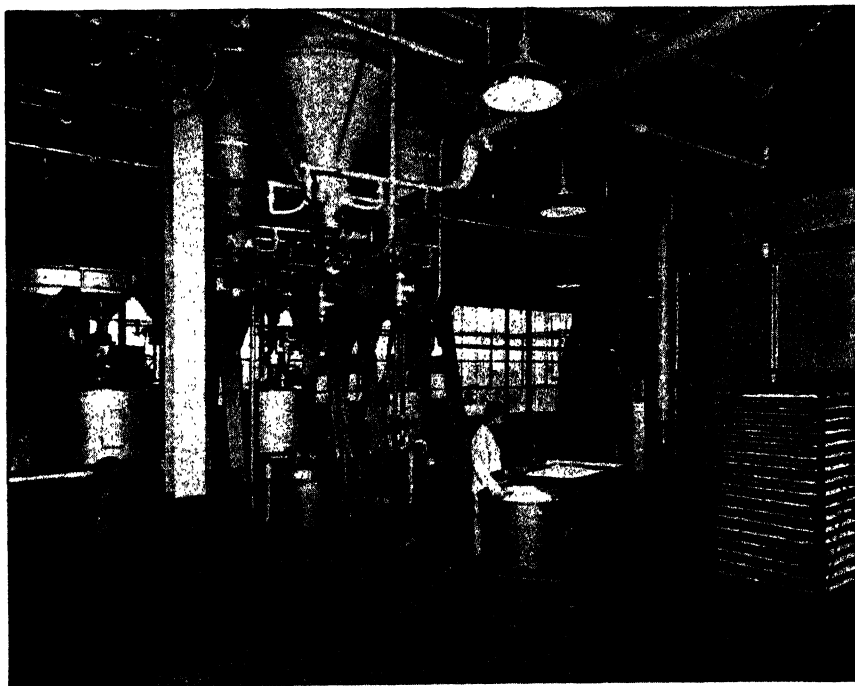
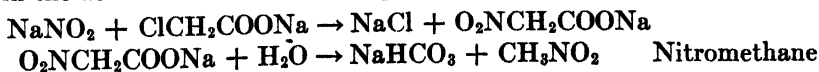


FIG. 34.—Production of crystalline nitroparaffin derivatives. (Courtesy of Commercial Solvents Corporation.)

Nitromethane is not obtained by direct nitration of methane; it is, however, a product of the nitration of ethane or propane. It may also be had from the action of sodium nitrite upon sodium chloroacetate:



The vapor phase nitration of ethane gives nitroethane (about 80%) and nitromethane (about 20%). Propane yields 1-nitropropane, 2-nitropropane, nitroethane, nitromethane, carbon dioxide, water, etc.

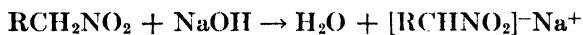


The aliphatic nitro compounds are pleasant-smelling, stable, colorless liquids, practically insoluble in water. Their boiling points are much higher than those of the isomeric nitrites. Mononitro compounds above nitromethane are not explosible.

### REACTIONS OF NITRO COMPOUNDS

(1) *Reduction to amines.* See page 305.

(2) *Salt formation.* Primary and secondary nitro compounds have respectively the following formulas:  $\text{RCH}_2\text{NO}_2$ ,  $\text{R}_2\text{CHNO}_2$ .\* In each of these types the hydrogen adjacent to the nitro group is active (as in those cases in which we have an adjacent carbonyl group). These nitro compounds will form salts with a strong base:



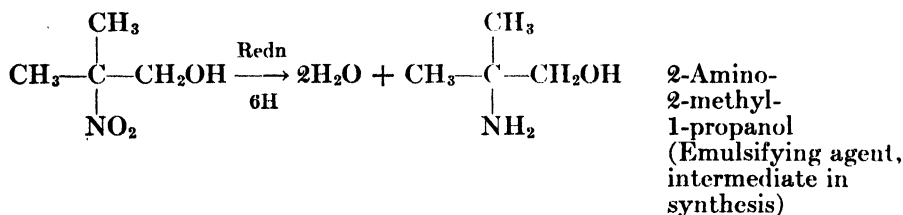
(3) *Action of a strong acid.* A primary nitro compound when heated with a strong mineral acid undergoes a complex reaction the products of which are an organic acid and a hydroxylamine salt:



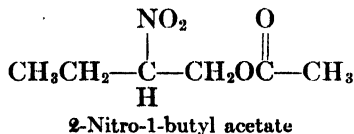
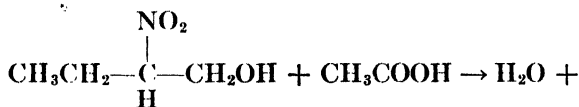
(4) *Formation of nitrohydroxy compounds* by reaction of nitro compounds with aldehydes in presence of a base.



(5) *Additional reactions.* (a) The reduction of the nitrohydroxy compounds gives aminohydroxy compounds.

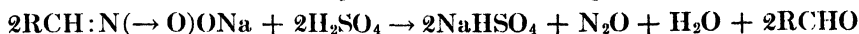


(b) The nitro alcohols yield esters in the customary way.



\* For structure of the nitro group, see page 445.

(c) Salts of primary and secondary nitroparaffins react with an excess of mineral acid to yield aldehydes and ketones, respectively, in good yield.



**Uses.** The nitroparaffins are useful solvents for shellac, rubber, and cellulose derivatives, and in addition are relatively non-toxic and less inflammable than some lacquer solvents now in use. It is expected that they will be widely used as solvents. Because of the large number of reactions possible to the nitroparaffins there is little doubt of their wide use as intermediates in chemical synthesis. See Reference 14, page 300.

TABLE 27.—ALIPHATIC NITRO COMPOUNDS, ETC.

Name	Formula	M.p., °C.	B.p., °C.	Sp.g., 20°/20°
Nitromethane.....	$\text{CH}_3\text{NO}_2$	— 29	101.2	1.139
Nitroethane.....	$\text{C}_2\text{H}_5\text{NO}_2$	— 90	114.0	1.052
1-Nitropropane.....	$\text{C}_2\text{H}_5\text{CH}_2\text{NO}_2$	—108	131.6	1.003
2-Nitropropane.....	$\text{CH}_3\text{CH}(\text{NO}_2)\text{CH}_3$	— 93	120.3	0.992
2-Nitro-1-butanol.....	$\text{C}_2\text{H}_5\text{CH}(\text{NO}_2)\text{CH}_2\text{OH}$	— 47 to —48	105	
2-Nitro-2-methyl-1-propanol.....	$\text{CH}_3\text{C}(\text{CH}_3)(\text{NO}_2)\text{CH}_2\text{OH}$	90-91	94.5-95.5	
2-Amino-1-butanol.....	$\text{C}_2\text{H}_5\text{CH}(\text{NH}_2)\text{CH}_2\text{OH}$	— 2	178	0.944
2-Amino-2-methyl-1-propanol.....	$\text{CH}_3\text{C}(\text{CH}_3)(\text{NH}_2)\text{CH}_2\text{OH}$	30-31	165	0.934

### REVIEW QUESTIONS

- Write equations showing the synthesis of acetonitrile from: (a) MeOH; (b) Acetic acid.
- Indicate by the use of equations three different methods of preparation of propanenitrile.
- Under what conditions would propanenitrile yield:
  - Propionic acid;
  - Propionamide?
- Make a chart showing the relationship of Methyl cyanide, Ethylamine, Acetamide, Acetic acid, Acetaldehyde.
- Write parallel equations for four reactions of HCN and Methyl cyanide which show that these compounds belong to the same class.
- Write equations showing the methods of obtaining primary and secondary amines from nitriles and isonitriles.
- Show by equations the synthesis of: (a) Propyl-N-methylurethan; (b) Ethylurea.
- Summarize by the use of equations the mode of preparation of cyanides, isocyanides, isocyanates, thiocyanates, and isothiocyanates.
- How has the relative position of the sulfur atom in thiocyanates and isothiocyanates been determined?
- In what respects is the chemistry of cyanogen similar to that of: (a) Methyl cyanide? (b) Chlorine?
- Summarize in equations the synthesis and reactions of calcium cyanamide.
- What reactions of organic compounds may be used to convert nitrogen to ammonia?
- How might cyanogen be obtained from ammonium oxalate? How does this synthesis help to establish the structure of cyanogen?
- Show how it is possible to synthesize acetic acid from methyl alcohol by methods given in this chapter.
- Why does the presence of either base or acid speed the hydrolysis of a nitrile?

16. What reactions given in connection with HCN favor the nitrile structure for this compound rather than the isonitrile structure?
17. What is the valence of carbon in the older formula for isocyanides? What is the valence for carbon in the modern formula?
18. Fill in the blanks below with names of the proper compounds:

Carbonic acid	{	acid chloride.....
		monoamide .....
		diamide .....
		nitrile .....

19. What is the relationship of cyanamide to carbamic acid? to cyanogen chloride?
20. Should potassium cyanide be written  $\text{KN}'$  or  $\text{KCN}$ ? Why?
21. Is the name cyanamide a rational one for the compound it represents? Why?
22. Write equations showing reactions of methyl isothiocyanate with ethyl alcohol and with ethylamine.
23. Suggest a method of separating a nitrile from the corresponding isonitrile. It is permissible to destroy either compound.
24. Show the synthesis of a nitrile from another organic compound by a method which: (a) Lengthens a carbon chain; (b) Does not lengthen the carbon chain.
25. List the physical properties which distinguish a nitrile from an amide; from an isonitrile.
26. Discuss the use of isocyanates in the identification of alcohols and primary amines.
27. Write two equations for the preparation of semicarbazide. For what may this compound be used?
28. What product might be formed by the action of cyanic acid upon semicarbazide?
29. Show by the use of equations four different methods for increasing the length of a carbon chain.
30. Show by the use of equations three different methods for removing one or more carbon atoms from a chain.

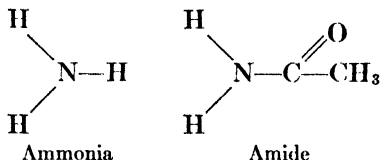
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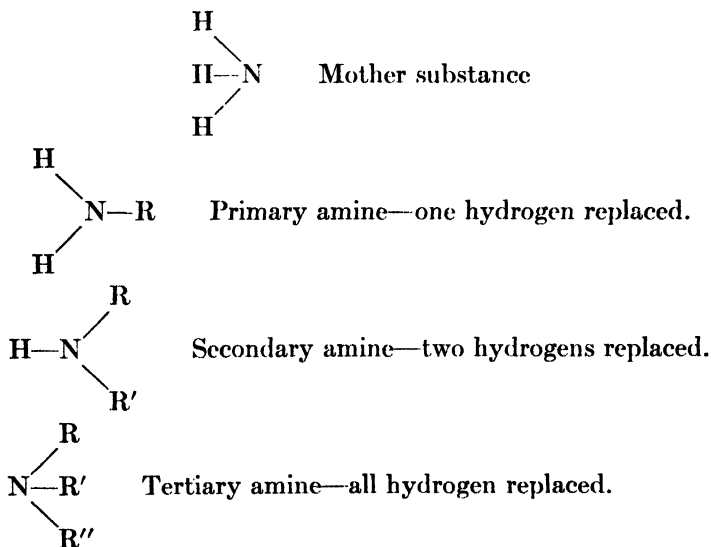
## CHAPTER XVI

### AMINES

When studying the acid amides we noted that these compounds are ammonia derivatives. They represent ammonia with one or more of its hydrogen atoms replaced by acyl groups:



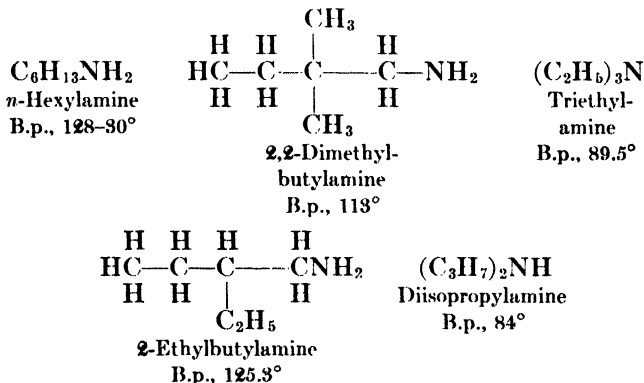
The amines are also ammonia derivatives; they are C, H, N, compounds obtained from ammonia by replacement of one, two, or three of its hydrogens by *alkyl groups*. In this way the following types of compounds arise:



The designations primary, secondary, etc., have already been used in naming in other series. The student will recall, for example, that in the primary, secondary, and tertiary alcohols we find one, two, and three hydrogens, respectively, of methyl alcohol replaced by alkyl groups (see page 95)

Since the alkyl groups may be either the same (simple amine) or different (mixed amine), the secondary and tertiary amines display metamerism, as is shown by the following examples of amines, all of which have the molecular formula  $C_6H_{15}N$ .

**Metameric Amines,  $C_6H_{15}N$ .** The method of nomenclature is illustrated in the naming of these compounds.



Distribution of carbon atoms in short chains lowers the boiling point in this series as with the alcohols and other series (note the exhibit above).

**Occurrence.** Amines and their derivatives are well distributed in nature. Methyl- and ethylamine are found in herring brine. Trimethylamine is found in this source, and is also obtained from distillation of the molasses residues from the beet sugar industry. The di- and tri-methylamines result from decay of fish.

**Physical Properties.** Methylamine, dimethylamine, and trimethylamine are gases, quite water-soluble, the first having strong ammoniacal odor, while the last two may be said to have a “fishy” odor. They are inflammable. Since the compounds derive from ammonia and hydrocarbons, we would expect them to have low density; such is the case. Higher amines are liquids or colorless solids. They show decreasing solubility in water with rising molecular weight.

**Basic Character of Amines.** The resemblance of the amines to ammonia is more than formal. Methylamine cannot be told from ammonia by odor; it fumes with hydrogen chloride as does ammonia, is exceedingly soluble in water, forming thereby a solution which is alkaline to litmus, and which precipitates the hydroxides of metals.\* The solution neutralizes acids, forming water-soluble salts, similar to the corresponding ammonium salts. All of these properties are common to ammonia. A review of the chemical reactions in the following sections shows still further likeness between amines and ammonia. The amino group is very important in

\* Methylamine was first made by Wurtz in 1848. It was distinguished from ammonia by reason of the fact that it burns in air.

organic chemistry, imparting desirable qualities when properly combined with other functions. Many compounds important in biochemistry are derived from amines. Physical properties of members of the various types are shown in the following table.

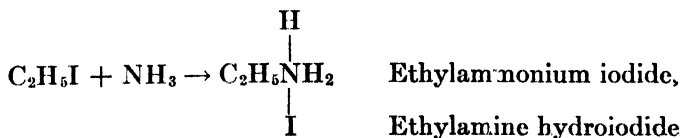
TABLE 28.—PRIMARY, SECONDARY, AND TERTIARY AMINES

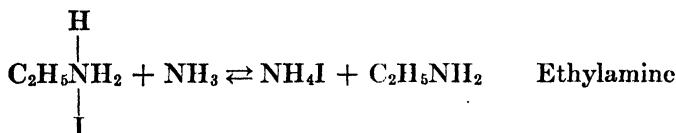
Name	Formula	M.p., °C.	B.p., °C.	Sp. g., 20°/4°	Ht. of comb.	K of ionization
Ammonia.....	NH <sub>3</sub>	- 77.7	- 33.4	0.817 <sup>-79</sup>	.....	1.82 × 10 <sup>-5</sup>
Methylamine.....	CH <sub>3</sub> NH <sub>2</sub>	- 92.5	- 6.5	0.699 <sup>-11</sup>	256.1	6.4 × 10 <sup>-4</sup>
Ethylamine.....	C <sub>2</sub> H <sub>5</sub> NH <sub>2</sub>	- 80.6	+ 16.6	0.689 <sup>15</sup> <sub>15</sub>	408.5	5.6 × 10 <sup>-4</sup>
Propylamine.....	C <sub>3</sub> H <sub>7</sub> NH <sub>2</sub>	- 83.0	48.7	0.719 <sup>20</sup> <sub>20</sub>	558.3	4.7 × 10 <sup>-4</sup>
Isopropylamine.....	.....	-101.2	33-34	0.694 <sup>15</sup>	.....	.....
Butylamine.....	C <sub>4</sub> H <sub>9</sub> NH <sub>2</sub>	- 50.0	77.8	0.740 <sup>25</sup>	710.6	.....
Isobutylamine.....	Me <sub>2</sub> CHCH <sub>2</sub> NH <sub>2</sub>	- 85.0	68-9	0.736	713.6	3.1 × 10 <sup>-4</sup>
Sec. Butylamine.....	EtMeCHNH <sub>2</sub>	-104.0	66	0.724	713	4.4 × 10 <sup>-4</sup>
Tert. Butylamine.....	Me <sub>3</sub> CNH <sub>2</sub>	- 67.5	45.2	0.696	716	.....
Amylamine.....	C <sub>5</sub> H <sub>11</sub> NH <sub>2</sub>	- 55.0	104	0.766 <sup>19</sup>	.....	.....
Isoamylamine.....	(CH <sub>3</sub> ) <sub>2</sub> CHCH <sub>2</sub> CH <sub>2</sub> - NH <sub>2</sub>	.....	95	0.751 <sup>18</sup>	867	5 × 10 <sup>-4</sup>
Sec. Amylamine.....	PrMeCHNH <sub>2</sub>	.....	91-2	0.749	.....	.....
Tert. Amylamine.....	Me <sub>2</sub> EtCNH <sub>2</sub>	-105.0	77-78	0.731 <sup>25</sup>	.....	.....
Hexylamine.....	C <sub>6</sub> H <sub>13</sub> NH <sub>2</sub>	- 19	128	0.763 <sup>25</sup>	1022	.....
Heptylamine.....	C <sub>7</sub> H <sub>15</sub> NH <sub>2</sub>	- 23	155.1	0.777	1179	.....
Dimethylamine.....	Me <sub>2</sub> NH	- 96.0	7.4	0.680 <sup>0</sup>	417	4.9 × 10 <sup>-4</sup>
Diethylamine.....	Et <sub>2</sub> NH	- 38.9	56.0	0.712 <sup>15</sup> <sub>15</sub>	716.9	1.26 × 10 <sup>-3</sup>
Dipropylamine.....	Pr <sub>2</sub> NH	- 39.6	110.7	0.739	.....	1.02 × 10 <sup>-3</sup>
Diisopropylamine.....	.....	.....	84	0.722 <sup>22</sup>	.....	.....
Dibutylamine.....	Bu <sub>2</sub> NH	.....	159	.....	.....	.....
Diisobutylamine.....	.....	- 70.0	138.8	0.745	1348	4.8 × 10 <sup>-4</sup>
Diisoamylamine.....	.....	- 44	190	0.767	1660	9.6 × 10 <sup>-4</sup>
Trimethylamine.....	Me <sub>3</sub> N	-124.0	3.5	0.662 <sup>-5.2</sup>	578.6	7.4 × 10 <sup>-5</sup>
Triethylamine.....	Et <sub>3</sub> N	-114.8	89.5	0.729 <sup>20</sup> <sub>20</sub>	1037	6.4 × 10 <sup>-4</sup>
Tripropylamine.....	Pr <sub>3</sub> N	- 93.5	156.5	0.757	.....	5.5 × 10 <sup>-4</sup>
Tributylamine.....	Bu <sub>3</sub> N	.....	216	0.778 <sup>20</sup> <sub>20</sub>	.....	.....
Triisobutylamine.....	.....	- 21.8	191.5	0.764 <sup>25</sup>	1974	2.6 × 10 <sup>-4</sup>
NH <sub>4</sub> OD.....	.....	.....	.....	.....	.....	1.1-1.4 × 10 <sup>-5</sup>

## PREPARATION OF AMINES

(1) The *primary amines* are formed:

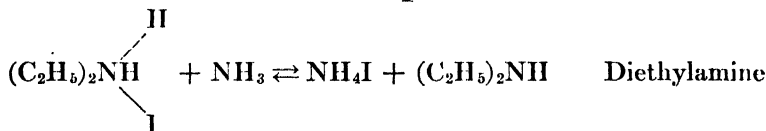
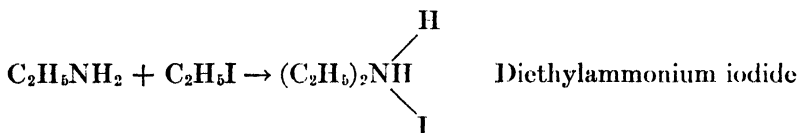
(a) By treatment of an alkyl halide with ammonia, either free or in a solvent. When free ammonia is used the materials must be heated in a sealed container. (Hofmann, 1851.)



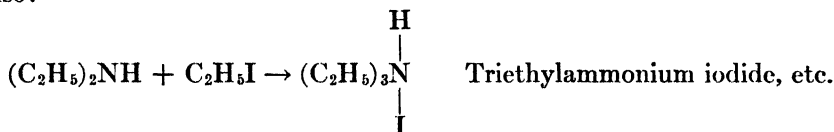


The reaction represents a competition between ammonia and the amine for possession of the hydrogen iodide. Ammonia is present in larger concentration than the amine and the reaction, while reversible, has its equilibrium point to the right. Amines are easily produced from such salts as ethylammonium iodide by treatment with a base. The isolation of the amine depends upon its properties. If a water-soluble liquid or gas, it may be distilled or steam distilled, or it may be extracted by an immiscible solvent; if the amine is insoluble in water (one of the higher amines) extraction is in order.

The reaction as initiated at (a) also gives secondary and tertiary amines by further action of the alkyl halide:



Also:



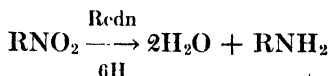
The final product of this reaction is a tetraalkyl salt,  $(\text{C}_2\text{H}_5)_4\text{NI}$ . Theoretically it appears simple to produce any type of amine by stopping the reaction at the proper point, but practically one obtains a mixture of all three types, primary, secondary, and tertiary, together with the tetraalkyl salt, which must then be separated. The action resembles the chlorination of methane, which gives a mixture of all the possible chlorination products. The mechanism of the reaction will be discussed later.

In commercial practice this method of preparation is successful because of the high efficiency of industrial distillation apparatus which permits a fairly clean separation of the amines. (There are also some instances in which the mixture of amines fulfils a useful purpose.) Alkyl chlorides are used in industry to make the amines as they cost less than the bromides or iodides.

It has recently been shown that liquid ammonia gives a much better yield of primary amine in this reaction than does an aqueous or alcoholic solution. The yield of primary amine increases with increase of molecular weight of the alkyl halide used, while the yields of the other types of amines fall off correspondingly. It is possible that this will become an important method of making primary amines.

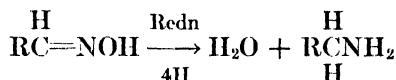
(b) The following methods are better than (a) as they do not yield mixtures of amines. They involve the reduction of various nitrogen compounds.

Nitroparaffin:

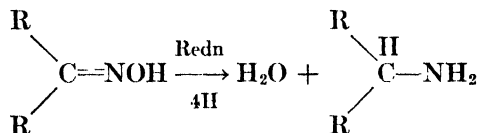


This method is more often used in the aromatic series than in the aliphatic, but as more aliphatic nitro compounds become available (see page 297) the reaction should gain importance in this series also.

Aldoxime:

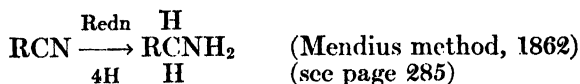


Ketoxime:



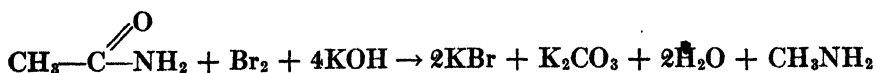
Oxime reduction is a very useful method for the production of pure amines. As reducing agents one may use zinc and acid, iron and acid, sodium and alcohol.

Nitrile:



High molecular weight primary and secondary amines are produced in industry by catalytic reduction of nitriles made by the action of ammonia upon fatty acids. Octadecylamine, for example, is made from stearic acid, a saponification product of fats. The long-chain amines have many uses (flotation agents, sterilizing agents, antioxidants).

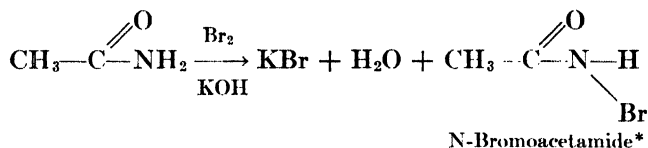
(c) Primary amines are obtained by the treatment of an amide having one more carbon than the desired amine, with bromine and potassium hydroxide. (Hofmann's reaction.)



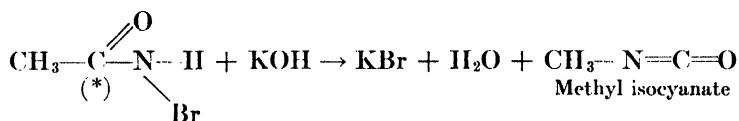


The reaction takes place in several steps.

(Step 1) Bromine replaces hydrogen of the  $\text{NH}_2$  group, forming a bromoamide:



(Step 2) The bromoamide on heating with alkali loses  $\text{HBr}$ , and rearranges to the isocyanate:



This rearrangement, commonly called the Hofmann rearrangement, has been studied for many years, and a number of theories have been proposed to explain it. The majority of these have assumed that in such a rearrangement the alkyl or R group parts company from the carbonyl carbon and exists for a time as a free radical. Recent work tends to show that this may not be true, and that the R group simultaneously gains attachment to nitrogen, and loses attachment to carbonyl carbon (marked with a star), without at any time being free.

(Step 3) Hydrolysis of the isocyanate yields the amine and carbon dioxide:



The Hofmann reaction forms the most practical laboratory method for the synthesis of primary amines,† utilizing cheap and available materials, giving good yields of amines.

(d) Primary amines are also produced in the Gabriel reaction (see page 537).

(e) When the vapors of methyl alcohol and ammonia are passed over thorium oxide at  $325\text{--}330^\circ$ , about one-third of the alcohol is converted to methylamine. Higher amines may be made in the same way from their alcohols. The process yields a mixture of primary, secondary, and tertiary

\* The capital N in the name signifies the attachment of the bromine to nitrogen.

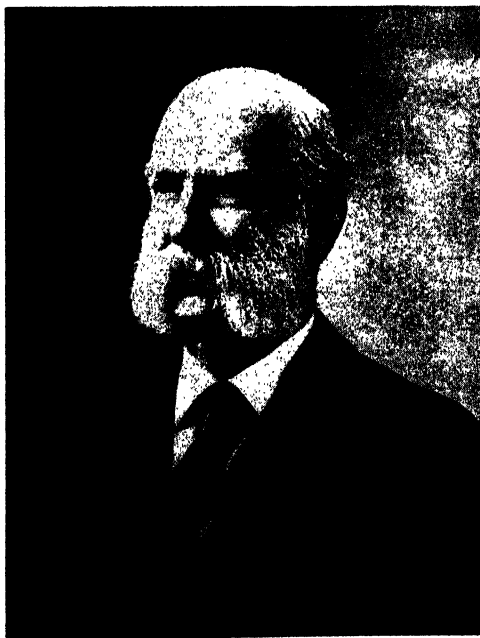
† We see by this equation that a primary amine may be made by the hydrolysis of the corresponding isocyanate when this is available; the Hofmann reaction combines the formation and decomposition of the isocyanate.

‡ The amides of acids having more than five carbon atoms yield nitriles having one less carbon atom. By adding an extra step to the reaction, the desired amines may be obtained.

WILLIAM H. PERKIN. (1838–1907, English.) After his accidental discovery of mauve in 1856, Perkin was for some time engaged in its commercial production. His interest in research continued and is manifested by the well known Perkin reaction, the synthesis of coumarin, a synthesis of alizarin. See *J. Soc. Chem. Ind.*, **26**, 858 (1907), *J. Chem. Soc. (London)*, **93**, 2214 (1908), Harrow, *Eminent Chemists of Our Time* (Van Nostrand, 1927, pp. 1, 241), *Ind. Eng. Chem. (News Edition)*, **16**, 608 (1938); also this book, page 682.



*Berichte*, **44**, 911 (1911).



*Journal of Chemical Education*.

JAMES M. CRAFTS. (1839–1917, American.) Crafts' work was divided between America and France. The Friedel-Crafts synthesis was developed in Paris. He worked with organic silicon compounds, density of halogens at high temperatures. He was head of the chemistry department, later president, of the Massachusetts Institute of Technology. See *J. Chem. Education*, **5**, 911 (1928), *ibid.*, **13**, 551 (1936); also Thomas, *Anhydrous Aluminum Chloride in Organic Chemistry*, Reinhold Pub. Corp., 1941; this book, pages 405, 575.

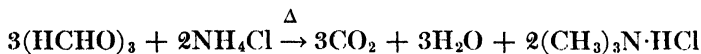
amines. Another synthesis of methylamine is from formaldehyde and ammonium chloride:



(2) *Secondary amines* are formed when alkyl halides react with ammonia, but this reaction is not a practical one for their preparation. Another method for their formation involves the use of aromatic compounds and will be taken up later (page 467). See also Reference 16, page 320.

(3a) *Tertiary amines* can be made by treating ammonia with an excess of an alkyl halide, subsequently with a base (page 304).

(b) A cheap synthesis of trimethylamine involves heating of a mixture of trioxymethylene and ammonium chloride:



(c) The tertiary amines form when tetraalkylammonium salts are heated:

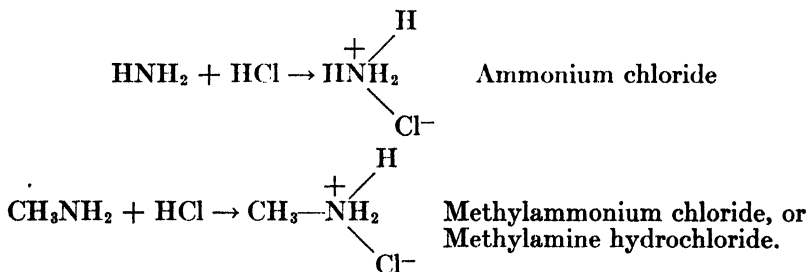


As we shall see later (page 312), tertiary amines may in some cases arise from the action of heat upon tetraalkylammonium hydroxides.

### REACTIONS OF AMINES

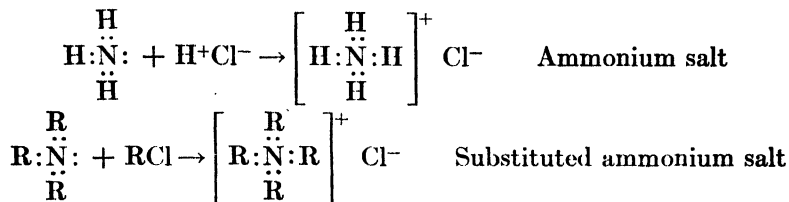
The reactions of all three types of amines are sufficiently alike to allow their presentation in one section. Such differences as we shall find depend in most cases upon the number of ammonia hydrogens which remain in the compound, and are easily understood.

(1) *Reaction with acids.* Amines act like ammonia toward acids, forming salts by direct addition:



The hydrochlorides and nitrates of amines are quite soluble in water; thus amines which are themselves insoluble in water may be brought into solution by the use of dilute HCl or HNO<sub>3</sub>. Treatment with a base regenerates the amine in all cases.

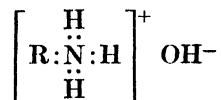
The ability of ammonia and amines to add reagents rests upon the possession of a lone pair of electrons by the nitrogen atom. A positive ion or group may add at this point, and in this way the ammonium or substituted ammonium ion is formed. The entire ammonium group becomes positive by virtue of the charge of the added atom or group. The fifth group or atom is held by electrostatic attraction, but the four groups or atoms about the nitrogen atom have covalent bonds.



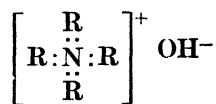
This type of reaction has been discussed before (page 126).

(2) *Action with water.* An amine adds water, forming a hydroxy-compound which, like ammonium hydroxide, is a base, ionizing in water to give  $\text{OH}^-$  ions. Bases formed in this way are stronger than ammonium hydroxide, and their strength reaches its maximum with the tetraalkylammonium hydroxides. Tetramethylammonium hydroxide,  $(\text{CH}_3)_4\text{N}\cdot\text{OH}$ , may serve as an example of these strong bases; it compares in strength with sodium- or potassium hydroxide.\*

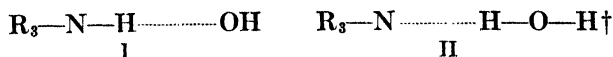
As the hydroxides of primary, secondary, and tertiary bases, while stronger bases than ammonium hydroxide, are still quite weak, it seems unwise to give them structures like the following:



since such a structure implies a strongly ionized compound. We could use a structure like this for a tetraalkyl hydroxide:



which, as said before, is a strong base. Since the only difference between the tetraalkyl base and the other bases is that the latter have hydrogen on the nitrogen and the tetraalkyl bases do not, chemists believe that this hydrogen is a bonding element between the nitrogen and the hydroxyl in the (largely) undissociated hydroxides of primary, secondary, and tertiary amines.

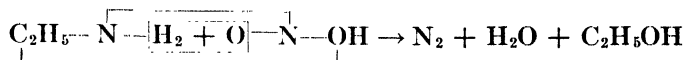


\* Note the similarly constituted sulfonium bases, page 131.

† From Taylor and Baker, *Organic Chemistry of Nitrogen*, Clarendon Press, Oxford, 1937.

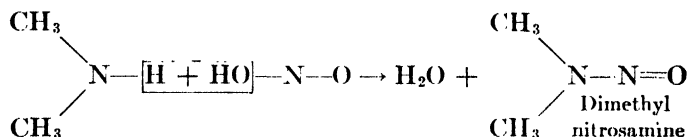


Primary amines by this treatment yield nitrogen gas and the corresponding alcohol, both of which products are easily identified, the former by inspection and the latter by a suitable test.



This reaction should be studied in connection with the reactions of nitrous acid with amides (page 228) and amino acids (page 238). These three examples will show that nitrous acid enables us to exchange  $\text{NH}_2$  group for  $\text{OH}$  in any compound.\* This method of making an alcohol is not a good one, however, on account of low yield.

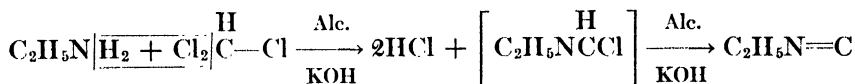
Secondary amines by action with nitrous acid yield compounds called nitrosamines (generally of a green or yellow color):



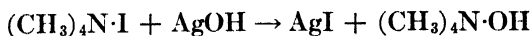
The nitrosamines are insoluble in water and are therefore easy to recognize.

Tertiary amines do not react with nitrous acid to give stable derivatives.

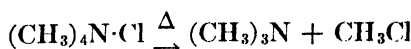
(6) *Carbylamine reaction.* Further tests for the identification of amines will be found on page 777. An additional test for primary amines is the "carbylamine reaction," which is performed by treating the amine with chloroform and alcoholic potash. An isocyanide is formed, having an unmistakable, intolerable odor. Secondary and tertiary amines do not follow this reaction.



(7) *Reactions of the tetraalkyl salts and bases.* (a) The tetraalkylammonium bases may be formed from the salts by treatment with moist silver oxide (silver hydroxide):



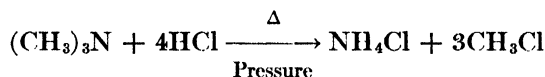
(b) Action of heat on tetraalkyl salts and bases. Tetraalkyl chlorides yield a tertiary amine and alkyl halide on being heated:



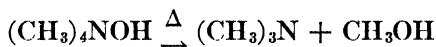
This is merely a reversal of the reaction by which the salt was formed. The alkyl halide liberated always contains the *smallest alkyl group* which

\* Methylamine does not yield methyl alcohol under the usual conditions. See Reference 15, page 320.

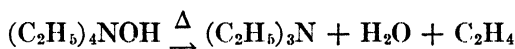
was attached to nitrogen. Incidentally, this is a **good way to make methyl chloride**, as trimethylamine is available from a cheap raw material (beet sugar waste). Heating with HCl gives  $\text{CH}_3\text{Cl}$ .



A tetraalkyl hydroxide yields a tertiary amine and an alcohol:



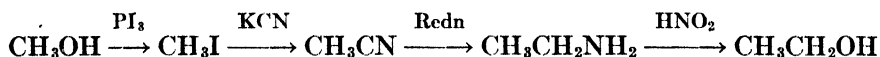
except in cases in which one of the alkyl groups has more than one carbon and is so constructed that it can form an olefin. For this it must have hydrogen on the carbon atom second removed from the nitrogen. In such a case the products are tertiary amine, water, and an olefin:



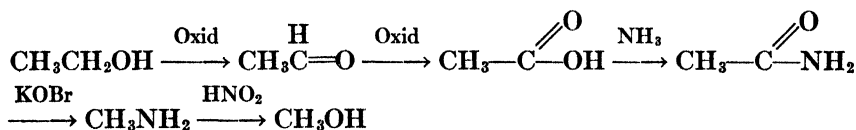
The *largest alkyl group* is thrown off in olefin form in this type of decomposition. In cases in which an olefin cannot be formed, the group is expelled as an alcohol as in the first example. The ethyl group very easily gives ethylene, so that the *largest group* is not *always* eliminated (see page 643).

#### GOING UP AND DOWN A HOMOLOGOUS SERIES

The reactions of the amines furnish methods of both adding carbons to and taking them from a chain, which may well be reviewed at this point (see also page 164). "Stepping up"—adding of one carbon atom, is accomplished as indicated in the following series:



"Stepping down" is carried out as shown schematically below:



These two sequences have the advantage of simplicity, but the last step of each gives a poor yield. A better method is known for this step, too difficult for presentation here. The series as shown run from "alcohol to alcohol," but also indicate the sequence from "alkyl halide to alkyl halide," "acid to acid," etc.

#### AMIDES VS. AMINES

The differences between amides and primary amines comprise the following:

1. Amines are made from ammonia and *alkyl* halides,  $R-NH_2$ .

Amides are made from ammonia and *acyl* halides,  $R-\overset{\overset{O}{\parallel}}{C}-NH_2$ .

2. Amines are not subject to hydrolysis, the nitrogen being firmly bound to carbon. They tend to add water to form ammonium bases.

Amides hydrolyze to their acids and ammonia; the presence of the carbonyl group loosens the attachment between carbon and nitrogen.

3. With nitrous acid, amines yield nitrogen and an *alcohol*.

Amides in this reaction give nitrogen and an *acid*.

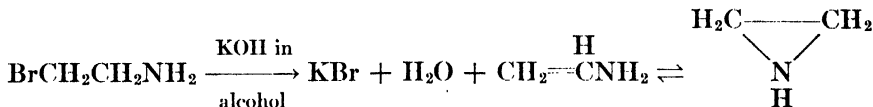
4. Amines are *alcohol* derivatives. } see page 316.  
Amides are *acid* derivatives. }

5. It may be noted that amines with acyl halides give substituted *amides*, while amides with alkaline hypobromite give *amines* with one less carbon atom. To this extent the two classes are interchangeable.

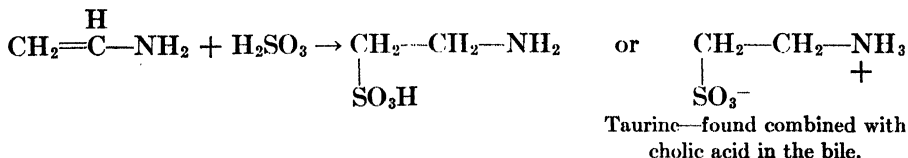
#### UNSATURATED AMINES, AMMONIUM COMPOUNDS

The unsaturated amines stand in the same relation to those already studied as ethylene, for instance, does to ethane. A few examples of the more important substances of this class are shown below.

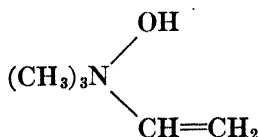
**Vinylamine**,  $C_2H_3NH_2$ . This is prepared from bromoethylamine and alcoholic potash:



This compound shows the additive properties of ethylene as its structure predicts. With sulfurous acid the important natural substance, **taurine**, is formed:

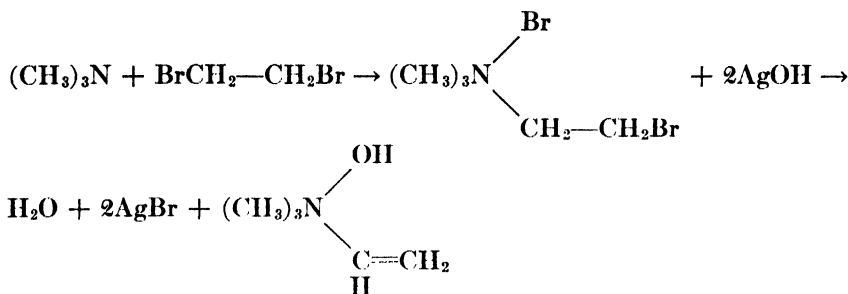


**Neurine**, or trimethylvinylammonium hydroxide:



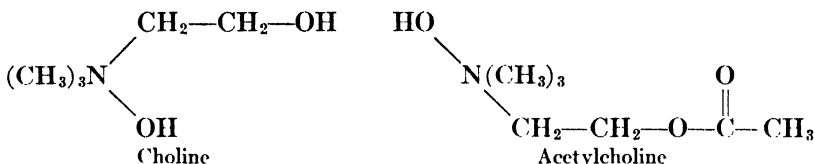
Neurine is prepared as shown in the following equation, from trimethylamine and ethylene dibromide:





Neurine is a natural product, found in putrefying meat.

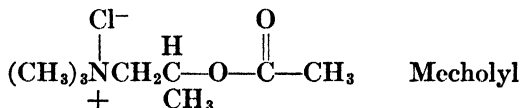
**Choline**, trimethyl- $\beta$ -hydroxyethylammonium hydroxide, can be made from water, ethylene oxide, and trimethylamine. It is found combined within the lecithins, substances which occur in animal tissues, especially in the brain.



**Acetylcholine.** Choline is not biologically active (that is, not in the sense considered here) but its acetyl derivative has a powerful physiological effect. This compound is formed at the nerve endings of the voluntary muscles when there is "will to action."\* The amount of substance so released is of course very small, but apparently it is the cause of muscle contraction.

The use of this substance in medicine is discouraged by its rapid hydrolysis to the inactive choline. Derivatives of choline which have been studied may possess two conflicting actions in the body. Both effects are common to quaternary ammonium bases, but vary with the nature and disposition of the substituting groups. One, called the muscarine effect, involves a stimulation of nerve endings of involuntary muscle; the other effect, somewhat antagonistic to the first, is termed the nicotine effect.

**Acetyl- $\beta$ -methylcholine chloride, mecholyl,**

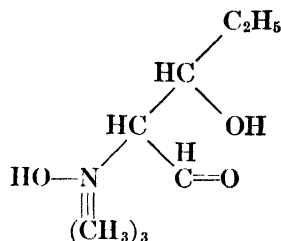


has been recommended for medical use because it has high muscarine action but very little nicotine effect. It causes slowing of heart beat, lowering of blood pressure, increased intestinal peristalsis. The compound is more stable than acetylcholine.

\* It also affects the sweat glands in cases of fright or shock, an action formerly thought due to adrenaline.

Neurine has physiological activity like that of choline, however much more pronounced. It is highly poisonous. Betaine (page 246) acts like choline when injected; taken by mouth it is inactive.

**Muscarine.** Muscarine is a highly toxic constituent of the toadstool and certain other plants. A suggested formula is:



Mushroom poisoning is caused by muscarine and other compounds, possibly similar in structure.

#### DIAMINES, POLYAMINES

Diamines, such as ethylenediamine,  $\text{H}_2\text{N}-\text{CH}_2-\text{CH}_2-\text{NH}_2$ , present no new points, either in their preparation or properties. The formulas of several diamines of importance are:

**Putrescine**, tetramethylenediamine, 1,4-butanediamine,  $\text{H}_2\text{N}-(\text{CH}_2)_4-\text{NH}_2$ . This compound is produced in the decay of animal matter.

**Cadaverine**, pentamethylenediamine, 1,5-pentanediamine,  $\text{H}_2\text{N}-(\text{CH}_2)_5-\text{NH}_2$ . Cadaverine, putrescine, and neurine belong to a class of compounds produced in the decay of nitrogenous matter, and sometimes called "*ptomaines*." The first two are not poisonous, while the latter is highly poisonous. Death by "ptomaine poisoning" has followed the use of decomposed meat or fish containing substances of this class; more commonly food poisoning is caused by the toxin of *B. botulinus*, an organism which occurs in canned corn, beans, etc., which have been incompletely sterilized in the canning operation. Other bacterial poisons may also be responsible for ill effects observed in certain cases.

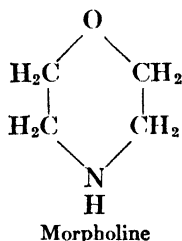
Polyamines which are now available in quantity include diethylenetriamine,  $\text{H}_2\text{NCH}_2\text{CH}_2\text{NHCH}_2\text{CH}_2\text{NH}_2$ , triethylenetetramine,  $\text{H}_2\text{N}(\text{CH}_2\text{CH}_2\text{NH})_2\text{CH}_2\text{CH}_2\text{NH}_2$ . These and similar compounds are used in the rubber, textile, and pharmaceutical industries.

#### ALKAMINES (ALKANOLAMINES)

The alkamines are amino alcohols.

**Ethanolamine**,  $\text{HOCH}_2\text{CH}_2\text{NH}_2$ , formed by action of ammonia upon ethylene oxide, is an interesting compound of this class. In its synthesis we get as by-products, di- and triethanolamine,  $(\text{HOCH}_2\text{CH}_2)_2\text{NH}$  and  $(\text{HOCH}_2\text{CH}_2)_3\text{N}$ . All three compounds are basic, the last especially so.

The commercial triamine is a mixture of the three compounds. It is used to make soaps, as an emulsifying agent, to make synthetic resins, as a reducing agent in silvering glass. Their soaps are especially good emulsifying agents, as they dissolve both in water and in organic solvents. Dehydration of diethanolamine gives morpholine; this is used as are the ethanolamines.\*



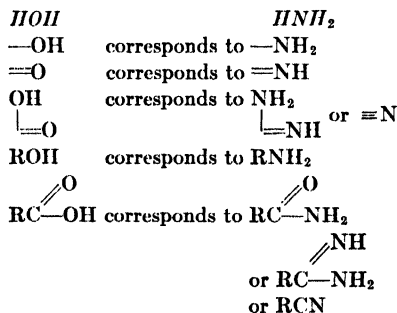
### USES OF AMINES

While there are many synthetic uses of amines as suggested by the reactions cited, not many direct ones are known. Di- and triamylamines have recently been recommended as inhibitors of corrosion of iron in acid media. Uses of the amino alcohols have been indicated. For additional information, see References, page 319.

### COMPARISON OF FORMULAS OF OXYGEN AND NITROGEN COMPOUNDS

The table on page 805 calls attention to the derivation of certain organic compounds from water and ammonia, respectively. From the close relationship of water and ammonia it follows that for organic compounds containing oxygen there will often be compounds of analogous structure which have nitrogen in place of the oxygen.

Examples.



Further examples of such correspondences will be found in Reference 13, page 320.

\* Compounds which have recently become available on the large scale are triisopropanolamine, diethylaminoethanol.

## REVIEW OF SUBSTITUTION REACTIONS AND IDENTIFICATION

In the previous pages a number of methods have been given for replacement of hydrogen by various radicals, and for exchanges between radicals.

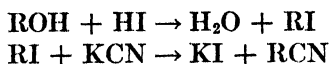
SUBSTITUTION CHART										
	H	Cl	Br	I	OH	COOH	CN	NH <sub>2</sub>	NO <sub>2</sub>	R
H	1	2	3	4	5	6	7	8	9	10
Cl	11	12	13	14	15	16	17	18	19	20
Br	21	22	23	24	25	26	27	28	29	30
I	31	32	33	34	35	36	37	38	39	40
OH	41	42	43	44	45	46	47	48	49	50
COOH	51	52	53	54	55	56	57	58	59	60
CN	61	62	63	64	65	66	67	68	69	70
NH <sub>2</sub>	71	72	73	74	75	76	77	78	79	80
NO <sub>2</sub>	81	82	83	84	85	86	87	88	89	90
R	91	92	93	94	95	96	97	98	99	100

Fig. 35.—Substitution chart.

The chart\* of Fig. 35 will help in reviewing this material. The following rules govern the use of the chart for home study or class assignments by the instructor:

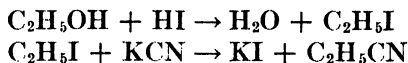
1. The atom or group in the vertical column is to be substituted for that in the horizontal line, i.e., number 47 calls for methods of replacing OH by CN.

General example:



\* This chart is adapted from the illustration used in an article by Dr. I. W. Wade, *J. Chem. Education*, 5, 72 (1928).

Specific example:



2. For squares in which the same symbols appear (1, 12, 23, etc.) give methods for identification.

Example: Square 23 would call for data that would identify an alkyl bromide; for example:

Density.....	greater than 1.
Odor.....	characteristic.
Beilstein test.....	positive.
Water solubility.....	slight.
etc.	

3. Give all conditions (temperature, use of catalysts, etc.) which are reported as necessary for the reactions used in synthesis and identification.

4. Work with saturated compounds first, then with unsaturated compounds, in so far as these have been discussed in the text.

### REVIEW QUESTIONS

- Write equations for the formation of the following amines: (a) Ethylamine (two methods); (b) Methyl ethylamine; (c) Triethylamine.
- How may the following substances be distinguished from each other:  $\text{C}_3\text{H}_7\text{NH}_2$ ,  $\text{C}_2\text{H}_5\text{NHCH}_3$ ,  $(\text{CH}_3)_3\text{N}$ ?
- Assign names to the following formulas. (a)  $(\text{CH}_3)_3\text{N}$ ; (b)  $(\text{C}_2\text{H}_5)_4\text{NBr}$ ; (c)  $\text{C}_2\text{H}_5\text{NH}(\text{CH}_3)$ ; (d)  $\text{C}_3\text{H}_7\text{N}(\text{CH}_3)\text{C}_2\text{H}_5$ ; (e)  $[(\text{CH}_3)_2\text{CH}]_3\text{N}$ ; (f)  $\text{C}_2\text{H}_5\text{NH}_3\text{I}$ ; (g)  $(\text{C}_3\text{H}_7)_4\text{NOH}$ .
- Show by equations the reactions of ethylamine with: (a)  $\text{HCl}$ ; (b) Acetyl chloride; (c)  $\text{CH}_3\text{I}$ .
- Indicate by equations the reactions used to make acetaldehyde from methyl chloride.
- Write equations showing the synthesis of dimethyl ether from: (a)  $\text{CH}_3\text{—}\overset{\text{O}}{\parallel}\text{C—NH}_2$ ; (b)  $\text{EtOH}$ .
- Summarize by a series of equations the essential points of difference between primary amines and amides.
- State how the following mixtures could be separated by chemical means. (a) *n*-propylamine, acetic acid, glycol; (b) *n*-butylamine, ethyl ether, *n*-heptane.
- How could the following compounds be distinguished from each other: (a)  $\text{CH}_3\text{—}\overset{\text{O}}{\parallel}\text{C—NH}_2$  and  $\text{C}_2\text{H}_5\text{NH}_2$ ; (b)  $\text{CH}_2\text{ClCH}_2\text{CH}_2\text{NH}_2$  and  $\text{C}_2\text{H}_5\text{NH}_2\text{Cl}$ ?
- The formula  $\text{C}_3\text{H}_9\text{N}$  represents several amines. Write formulas for the possible isomers, and tell how one could decide in a given case which compound was in hand.
- What would be formed upon heating: (a) Methyl-diethyl-propyl-ammonium chloride? (b) Methyl-diethyl-butyl-ammonium hydroxide?
- Can you cite any reaction of amines in which a C—N bond is broken?
- Show by electronic formulas the method of addition of methyl iodide to methylamine.
- Write equations for the synthesis of choline suggested in the text.
- In the light of what has been said about the strength of the bases formed by amines and water, what is the probable electronic formula for ammonium hydroxide?

16. You are to prepare ethylamine from ammonia and ethyl iodide. What other products might be formed? How would you decrease the secondary reactions?
17. Outline the series of operations which would be necessary for the identification of N-methylacetamide.
18. Make a table showing a comparison of the physical and chemical properties which would be observed while testing a solid amide and a solid primary amine.
19. What would be formed by heating trimethylethylammonium hydroxide?
20. What advantage and what disadvantage adhere to the Hofmann method for the synthesis of primary amines?
21. What properties distinguish a liquid primary amine from a liquid saturated hydrocarbon?
22. How does acetyl chloride react with the three amines,  $\text{RNH}_2$ ,  $\text{R}_2\text{NH}$ , and  $\text{R}_3\text{N}$ ?
23. Tell in detail how it can be shown that a given tertiary amine has two methyl groups and one ethyl group.
24. How many grams of ethyl iodide would be required to convert 20 g. of ammonia to tetraethylammonium iodide and  $\text{NH}_4\text{I}$ ? (Assume a 100% yield.)
25. List those reactions (tests) which serve to detect a primary amine. Which one would give the same apparent result when applied to an amide? What further test would allow one to distinguish an amide from a primary amine? What physical properties would be of assistance here?
26. Make a chart showing the structural formulas of the isomeric amines of molecular formula  $\text{C}_6\text{H}_{13}\text{N}$ . Illustrate by abbreviated equations how each amine reacts with  $\text{HNO}_3$ ;  $\text{CH}_3\text{COCl}$ ;  $\text{HCCl}_3$  and alcoholic potash;  $\text{HCl}$ ;  $\text{MeI}$ .
27. Discuss in some detail those amines which have a medical interest.
28. Three isomeric amines have the formula  $\text{C}_4\text{H}_{11}\text{N}$ . Upon treatment with nitrous acid, compound (A) shows no reaction, whereas (B) yields a yellow oil, only slightly water-soluble. (C) yields nitrogen and *n*-butyl alcohol. Tell all you can about the structures of (A), (B), and (C).
29. The liquid compound (A) dissolves in water giving a solution which is basic to litmus paper. The compound reacts with acetyl chloride to give a white solid. Treatment with chloroform and alkali yields a vile-smelling oil. Explain the probable nature of (A).
30. The compound (A) is an amine containing one atom of nitrogen and 16.09% nitrogen. When it is treated with an excess of methyl iodide a salt containing 55.46% iodine is formed. What are possible structures of (A)?
31. Analysis of a basic compound (A) which contains only C, H, and N, gives these figures: combustion of a 0.128 g. sample gives 0.2863 g. of  $\text{CO}_2$  and 0.1757 g. of  $\text{H}_2\text{O}$ . Treatment of another sample weighing 0.200 g. gives 37.95 cc. of nitrogen (at standard conditions). When (A) is treated with nitrous acid the compound (B) is secured. This reacts with sodium and with acetyl chloride, but not with ammoniacal silver nitrate solution. Upon oxidation it gives the compound (C) which does not affect Fehling solution, but yields a solid derivative with sodium bisulfite solution. (C) also reacts with phenylhydrazine, giving a solid compound of melting point  $26.6^\circ\text{C}$ . Discuss these experiments and propose a structural formula for (A).

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## CHAPTER XVII

# COMPOUNDS OF ARSENIC, PHOSPHORUS, SULFUR, AND METALS

## PHOSPHORUS AND ARSENIC

Besides nitrogen, whose alkyl compounds have been reviewed in preceding sections, the fifth group of the periodic system contains the elements phosphorus, arsenic, antimony, and bismuth, whose chemical properties might be expected to resemble somewhat those of nitrogen. Organic compounds containing these elements have been prepared, and some of them are important.

The alkyl derivatives of arsenic are called arsines; similar derivatives of phosphorus are the phosphines. Type formulas and nomenclature are the same as for the amines.

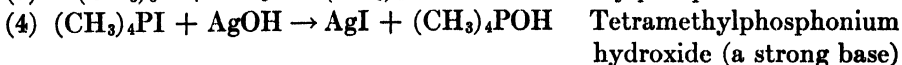
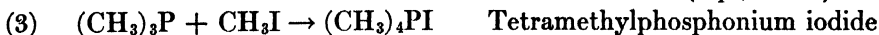
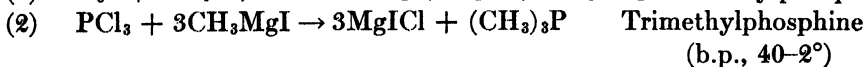
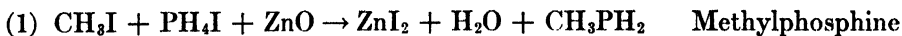
Examples:

$\text{CH}_3\text{NH}_2$   
Primary amine  
Methylamine  
(b.p.,  $-6.5^\circ$ )

$\text{CH}_3\text{AsH}_2$   
Primary arsine  
Methylarsine  
(b.p.,  $2^\circ$ )

$\text{CH}_3\text{PH}_2$   
Primary phosphine  
Methylphosphine  
(b.p.,  $-14^\circ$ )

**Preparation.** The following equations illustrate the preparation of several alkyl phosphines and phosphonium derivatives:

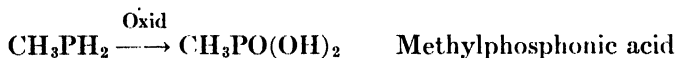


Equations (3) and (4) should be compared with the corresponding equations for the nitrogen derivatives (see Chapter XVI).

The arsines and derivatives of bismuth are prepared by special methods. Arsenic and phosphorus resemble nitrogen in the formation of tetraalkyl salts and bases, the latter being highly ionized, strong bases. The alkyl derivatives of phosphorus and arsenic differ from those of nitrogen in their ease of oxidation. While the amines are comparatively stable to oxidation, phosphines easily oxidize.



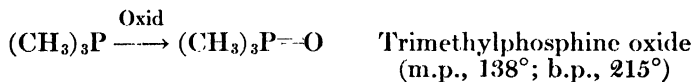
Primary phosphines in this way produce alkylphosphonic acids:



Secondary phosphines oxidize to dialkylphosphinic acids:

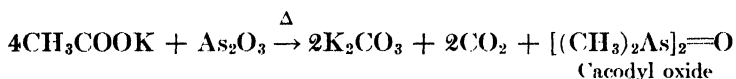


Tertiary phosphines yield phosphine oxides:

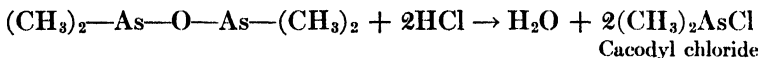


Phosphines are less basic than amines. The arsines are still less basic than the phosphines and are more highly oxidizable. The series of oxidation products shown for the phosphines occurs also for the arsines. The sodium salt of methylarsonic acid,  $\text{CH}_3\text{AsO}(\text{OH})_2$ , oxidation product of methylarsine, is used in medicine under the name of *Arrhenal*.

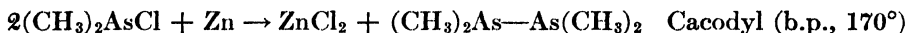
**Cacodyl.** When potassium acetate and arsenious oxide are heated together, a substance called cacodyl oxide\* is one of the products:



This is a liquid with an insupportable, vile odor. By treatment with hydrogen chloride, cacodyl chloride is obtained from it:



and the latter substance, when treated with zinc yields cacodyl:



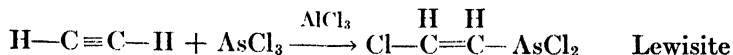
Cacodyl, tetramethyldiarsenic, is a poisonous liquid, spontaneously inflammable in air. It and its derivatives were extensively investigated by the chemist Bunsen in the years 1837-1843. At this time there was much interest in the preparation of free radicals (methyl, ethyl, etc.). The reactions of organic chemistry seemed to be reactions of radicals, and repeated attempts were made to isolate the radicals themselves. When Bunsen made cacodyl he thought that he had such a radical. Actually the molecular weight of the compound is twice that of the simple radical— $\text{As}(\text{CH}_3)_2$ , which he thought he had made.

**Cacodylic acid**,  $(\text{CH}_3)_2\text{AsO}(\text{OH})$ , is an oxidation product of cacodyl oxide. Its salts are employed in medicine.

\*The cacodyl products derive their name from a Greek root meaning "stinking." They have repulsive odors.



**Lewisite**,  $\text{ClC}=\text{C}-\text{AsCl}_2$ , and ethyldichloroarsine,  $\text{C}_2\text{H}_5\text{AsCl}_2$ , are examples of poisonous arsenic compounds used as "war gases." Lewisite is made by interaction of acetylene and arsenic chloride:



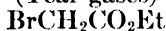
The equation shows the formation of "primary" Lewisite. The reaction gives also the secondary and tertiary substitution products,  $\begin{array}{c} \text{H} \quad \text{H} \\ | \quad | \\ (\text{ClC}=\text{C})_2\text{AsCl} \end{array}$  and  $(\text{ClC}=\text{C})_3\text{As}$ . The primary Lewisite is the desired compound, being far more active than the others. Heating with  $\text{AsCl}_3$  under pressure transforms secondary and tertiary to primary.

Lewisite has a multiple action as a war gas; it is injurious to the lungs, is a vesicant and a general poison. On hydrolysis it yields an oxide,  $\begin{array}{c} \text{H} \quad \text{H} \\ | \quad | \\ \text{ClC}=\text{CAsO} \end{array}$ , which also is a vesicant. Ethyldichloroarsine is a vesicant and lung injurant.

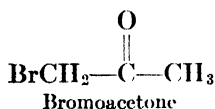
**War Gases.** Space limitations will not allow a full treatment of organic chemicals especially adapted for use in warfare. The following list shows some of the aliphatic compounds which have been proposed or used, grouped according to the principal effect secured in so far as this can be done. Compounds of the aromatic series appear on page 606.

*Lacrimators*

(Tear gases)



Ethyl bromoacetate



Cyanogen chloride  
(Lacrimator and systemic poison)

*Vesicants*

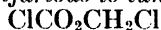
(Skin blistering agents)

Mustard gas (page 132)



Methyldichloroarsine

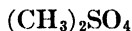
*Injurious to lungs*



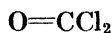
Chloromethyl chloroformate



Trichloromethyl chloroformate



Dimethyl sulfate



Phosgene



Chloropicrin

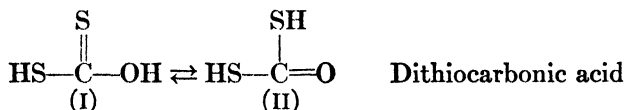
## SULFUR

The element sulfur plays an important part in organic chemistry. On account of the chemical likeness of sulfur and oxygen, there are for a great many oxygen compounds corresponding sulfur derivatives, somewhat analogous in method of preparation and mode of reaction. Advantage has been taken of this fact in this book to include the sulfur compounds along with their oxygen analogs, and to discuss them together.

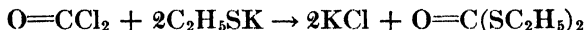
The following sulfur compounds have been treated in this way:

Thioalcohols and thioethers (pages 113, 130); Thio- and dithioacids (page 181); Sulfones and sulfoxides (page 130); Thiourea (page 275); Thio-cyanates and isothiocyanates (page 292).

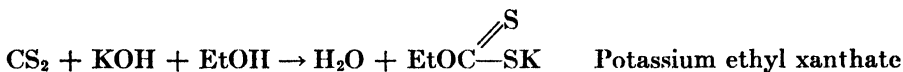
Di- and trithiocarbonic acids will be discussed briefly.



**Dithiocarbonic Acid.** This acid is not known free, but organic derivatives of both tautomeric forms have been made. Alkyl derivatives of form (II) result from action of phosgene upon mercaptides:

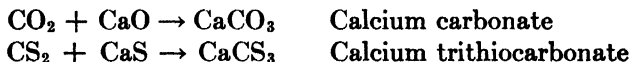


Derivatives of form (I) are more important. Those of the form  $\text{R}-\text{O}-\text{CS}_2\text{M}$  (M = metal) are known as xanthates. They are formed when carbon disulfide reacts with an alcohol and a base:



The copper salt of xanthic acid is yellow in color and insoluble in water. Hence the above reaction forms a delicate test for small amounts of carbon disulfide. Cellulose, when treated with carbon disulfide and alkali, goes into solution as cellulose xanthate. A water solution of the salt is known as viscose. It is used in paper sizing and to make Rayon.

The xanthates (ethyl, butyl, amyl) are used in ore flotation. Xanthates have also been used as soil fungicides. Inorganic salts of *trithiocarbonic acid*  $(\text{HS})_2\text{C}=\text{S}$  are well known, being formed from carbon disulfide and sulfides, just as are carbonates from the action of oxides and carbon dioxide:



The organic derivatives, while well known, are not of particular interest.

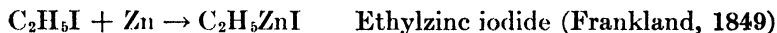
**Silicon.** Because silicon belongs to the same group of the periodic system as does carbon, it might be inferred that for all carbon compounds there should be corresponding derivatives of silicon. This is true to a certain extent, but the analogy falls down when we consider carbon compounds with

long chains, because silicon does not unite with itself as does carbon to form these chains. The number of organic silicon compounds is therefore limited. The preparation of a silicon compound is shown in the next section.

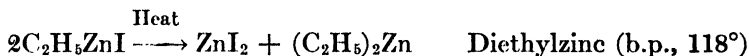
#### ORGANOMETALLIC COMPOUNDS\*

The reaction between alkyl halides and magnesium to form the Grignard reagent,  $R-Mg-Hal$  has been mentioned in a former chapter (see page 83).† Other metals than magnesium may react to form such derivatives, notably the element zinc.

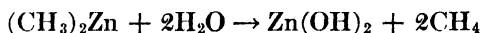
**Zinc Compounds.** The reaction of zinc with an alkyl halide may take the following course:



or a dialkyl derivative of zinc may be formed by heating the zinc alkyl halide:

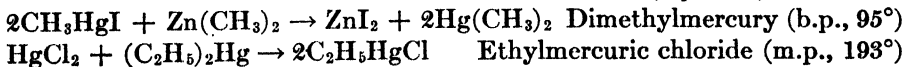
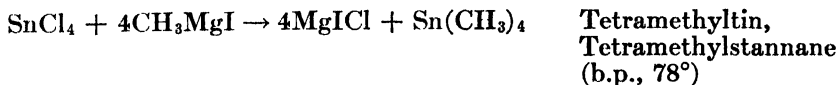
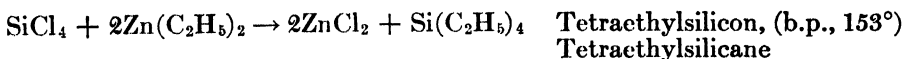


Zinc alkyls react with water (or alcohols) to form the saturated hydrocarbons corresponding to their alkyl groups:



They likewise react with aldehydes and ketones, allowing the formation therefrom of secondary and tertiary alcohols. These reactions, and others of which they are capable, formerly led to their use as synthetic agents, in spite of the practical difficulties involved in handling compounds so easily oxidized that they take fire in the air. They have now been displaced in synthetic work by the Grignard reagents and have principally a historical interest.

**Alkyl Compounds.** Alkyl derivatives of silicon, tin, mercury, etc., are conveniently prepared from the zinc or magnesium alkyls, and also by other methods.

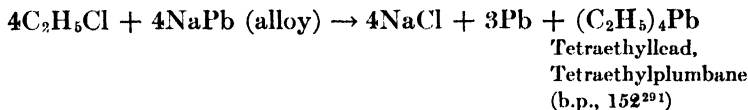


Mercury dialkyls, such as dimethylmercury, are liquid. They are highly poisonous. The monoalkyl mercuric salts are solids. Ethylmercuric chloride is used in dusting powders as a fungicide.

\* In a sense, such compounds as copper acetylide belong in this classification, but salts of acids, alkoxides, etc., in which the metallic atom is not joined directly to carbon, are not a part of the group.

† For more detailed treatment of the Grignard reaction, see Chapter XXIX.

**Tetraethyllead**,  $\text{PbEt}_4$ , is a component of "Ethyl gas" functioning therein as an antiknock compound.



Its function in the ethyl gas is to delay the explosion wave in the engine, preventing detonation of the charge. It is customarily blended with ethylene bromide (see page 88). Tetraethyllead is a highly toxic compound, being absorbed both by the lungs and through the skin. Lead poisoning follows. The chemistry of the organometallic compounds cannot be considered in any detail in this book; however, the tremendous importance of the magnesium compounds in the Grignard reaction makes it desirable to consider analogous derivatives of other metals momentarily, as we have done. The Grignard reaction is carried out with aromatic compounds as well as aliphatic, and for that reason its consideration is delayed until the aromatic series shall have been studied.

### REVIEW QUESTIONS

1. Show by means of equations and discussion the chemical likeness and difference of trimethylamine, trimethylphosphine, and trimethylarsine.
2. Write equations for the formation of cacodyl bromide. How could cacodyl be made from it?
3. Write equation showing how sodium propyl xanthate could be made.
4. Write equations for the action of diethylzinc with: (a) Water; (b) Alcohol.
5. How may tetramethylsilicon be made?
6. Write equations for the synthesis of: (a) Tetraethyltin; (b) Diethylmercury.
7. Show by equations how one might prepare: (a) Dimethylphosphine; (b) Triethylphosphine; (c) Methylarsine.
8. What uses can you suggest for poisonous compounds of arsenic, aside from employment as war gases?
9. Write structural formulas to fit the following names. (a) Diethylphosphine; (b) Tetraethylphosphonium bromide; (c) Di-*n*-propylphosphinic acid; (d) Ethanearsonic acid; (e) Triethylarsine oxide.

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## CHAPTER XVIII

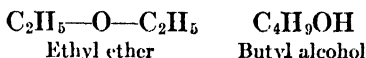
### OPTICAL ACTIVITY

**Isomerism. Résumé and Extension.** Several different kinds of isomerism have been studied up to this point. These have included:

(1) *Structural Isomerism.* This takes in:

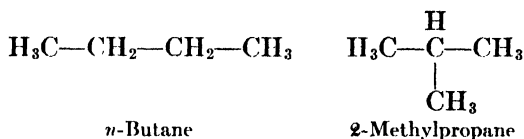
(a) Functional isomerism, such as occurs with any two compounds which by accident have the same molecular formula, but have different functional groups.

Example:



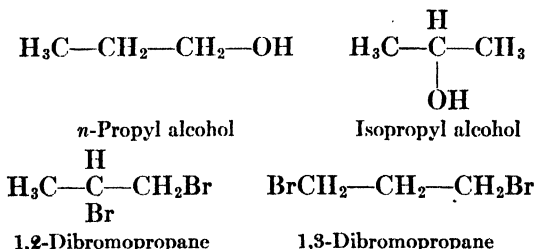
(b) Chain isomerism.

Example:



(c) Position isomerism; cases in which the isomers are alike except for the location of substituting atoms or groups.

Examples:



(2) *Stereoisomerism or Space Isomerism* (from Greek, *Stereos*, a solid). This type of isomerism depends upon the three-dimensional arrangement of atoms in the molecule. It includes:

(a) Geometrical or *cis-trans* isomerism. One form of geometrical isomerism has already been noted (pages 59, 263). This occurs in compounds with double bonds and is due to the fact that rotation of atoms is restricted in such cases. In the examples shown on p. 328, I and II appear

to be different compounds, since the X groups are in one case on the same side of the molecule, and in II are on the opposite sides.

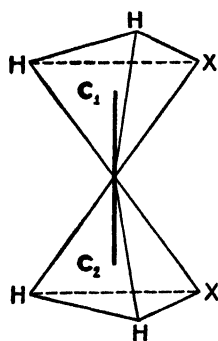


FIG. 36.

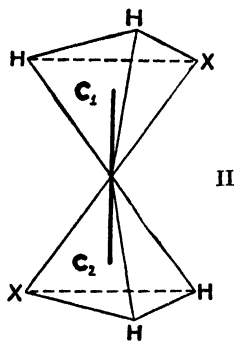
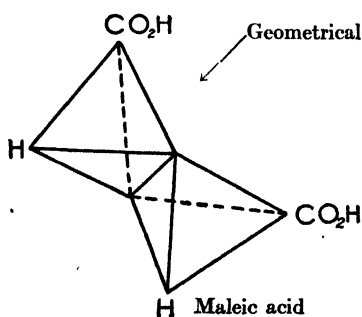


FIG. 37.

FIGS. 36, 37.—Identical molecules.

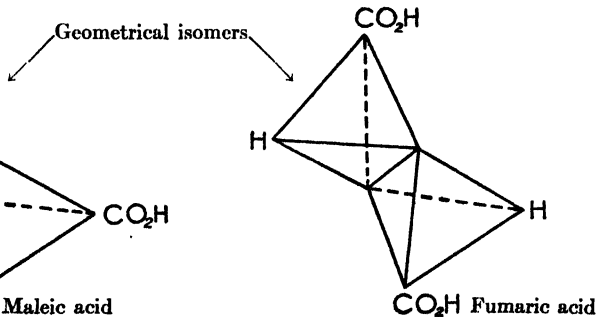
Actually no such isomers have ever been made. The natural conclusion is that the carbon atoms,  $C_1$  and  $C_2$ , are able to rotate about the axis formed by the bond between them; thus they can assume all possible positions which lie between the two extremes pictured here, or, practically speaking, we have one compound and not two or more. We shall later come to cases in which free rotation is impossible for atoms joined by a single bond. This occurs when the X groups are so large that they will not “clear” each other (see page 421).

When two atoms are joined by a double bond, it is apparent that free rotation of the atoms is no longer possible; many cases of isomerism of this type of compound are known. One which has been given is that between fumaric and maleic acids (page 262).



Maleic acid

FIG. 38.



Fumaric acid

FIG. 39.

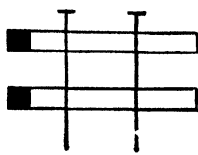
A simple way to picture the relationships is given on p. 329. In (I) two boards are shown joined by a single nail. Free rotation can occur, and it is impossible to have two different arrangements which are permanent. In

(II) and (III) the boards are fastened by two nails. Free rotation is not allowed, and hence there are the two possible different arrangements shown.



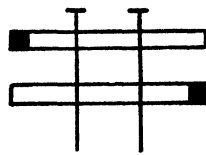
(I)

FIG. 40.



(II)

FIG. 41.



(III)

FIG. 42.

Other examples of this kind of isomerism will be shown in later chapters, also other types of geometrical isomerism will be given.

(b) Optical isomerism. Distinction between geometrical isomers is usually not difficult. They differ in physical properties (melting point, boiling point, solubility, density) and in some cases are quite different in chemical properties as well. In optical isomerism we have a much more subtle phenomenon. Two optical isomers will have the same chemical reactions (*in vitro*\*) and will be alike in the physical properties just mentioned and in other physical properties. They can often be distinguished by differences in physiological action (action *in vivo*), however the best method of setting them apart is by means of their action on plane polarized light.

**Optical Activity.** In ordinary light the vibrations occur in all planes, at right angles to the line of propagation. Plane polarized light has its vibrations confined to one plane. If an optical isomer be placed in the path of

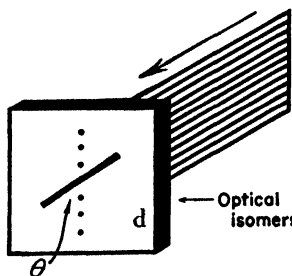


FIG. 43.

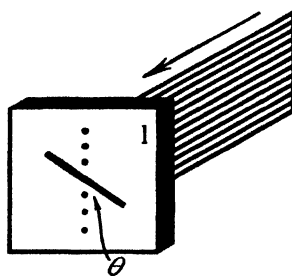


FIG. 44.

FIGS. 43, 44.—Rotation of plane polarized light by the optical isomers *d* and *l*. The dotted line shows original plane of vibration and the heavy line shows the rotation of the plane through the angle  $\theta$ .

plane polarized light, the plane of vibration will be rotated or twisted to the right or left. If we think of the light as vibrating in a vertical plane, the effect will be as shown above; on emergence from the optical isomer *d* or *l* (shown in the form of a thin plate) the plane of vibration is rotated to the right or left.

\* The expression "*in vitro*" refers to the use of laboratory apparatus; the corresponding expression "*in vivo*" refers to the use of a living organism.



The ability to rotate the plane of polarized light is called *optical activity*. Compounds which cause rotation to the right are termed dextrorotatory (*d*) while those which rotate left are called levorotatory (*l*). The instrument used to create plane polarized light and study its effects is the polarimeter, which is shown below in diagram.

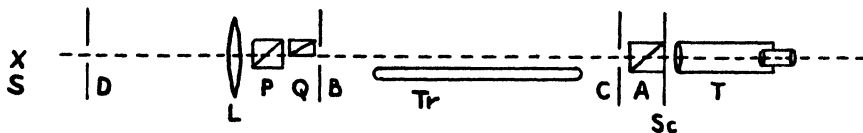


FIG. 45.—Diagram of Polarimeter.

**Polarimeter.** Plane polarized light is produced by the use of a Nicol prism of calcite (crystalline calcium carbonate), or a "Polaroid" plate. Light which passes through the prism vibrates in but one plane, and if a second prism is placed beyond the first with its principal plane in line with that of the first, the light will pass. If, however, the second prism is

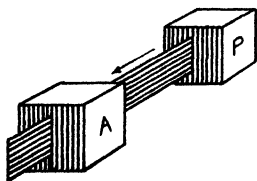


FIG. 46.

FIG. 46.—Parallel prisms. Transmission of plane polarized light.

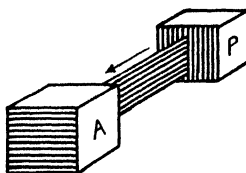


FIG. 47.

FIG. 47.—Crossed prisms. Plane polarized light blocked at prism A.



FIG. 48.—Polarimeter.

"crossed," that is if its principal plane is at right angles to that of the first, no light can pass. In the diagram, S is a light source, usually a sodium flame, which gives practically monochromatic light; B, C, and D are apertures to sharply define the beam of light; L is a converging lens and T the observer's telescope.

P is the polarizing Nicol and Q is a smaller Nicol which covers half of P. One-half of the field of view receives polarized light which has come through P and Q, while the other half of the field gets light from P only. P and Q have their principal planes set at a small angle to each other. The analyzing Nicol, A, is set in a mounting which can rotate, the amount of rotation being shown on the circular scale, Sc. Now if the analyzing Nicol A is "crossed" with P, one-half of the field looks black. A small movement of A crosses it with Q and then the other side of the field is black.

The zero point is midway between these two positions; both halves of the field are of the same brightness. Tr is a covered light-tight trough in which the tube of solution may be placed for examination.

*Variables affecting rotation.* When a solution of optically active compound is placed in Tr, we note that the two halves of the field are unequally bright. A must be rotated a certain number of degrees to restore the zero point condition. This angle is the *degree of rotation*. Its magnitude depends upon (a) the number of molecules through which the light passed, hence varies directly with the concentration of the solution and the length of the column of solution, (b) the nature of the substance, (c) the temperature.

**Specific Rotation.** In order to compare the activity of different substances we employ their specific rotations. Specific rotation is the rotation per decimeter of solution divided by the number of grams of substance per cc. of solution.

$$[\alpha]_D^{20} = -36.0^\circ$$

The symbol above shows that the specific rotation of the substance, taken at 20° with a sodium flame as source (D refers to the principal wave lengths of the sodium flame, the D lines of the solar spectrum) was 36° left. Dextro-rotations are marked (+). The specific rotation varies with concentration of solution and with the wave length of the incident light, also the nature of the solvent used. The molecular rotation is the specific rotation times the molecular weight, divided by 100.

**Optically Active Compounds.** The polarization of light was first noted in 1808 (Malus), and in 1811 Arago found that quartz is optically active, some crystals being dextrorotatory, others levorotatory. Other optically active crystals were found later.

Quartz occurs in two kinds of crystals which have the hemihedral facets on opposite sides of the crystal; (that is the crystals are mirror images of each other). Such mirror-image crystals are called enantiomorphs; their peculiar relationship to one another was offered as an explanation of the opposite rotations caused by the two crystals (1820, Herschel).

We have found by X-ray analysis that the atoms in such crystals have a definite arrangement; this is evidently responsible for the optical activity, for if the crystalline form is destroyed, as by solution, optical activity disappears.

With the organic compounds we are to discuss the case is entirely different. These preserve their optical activity when fused or in solution, or even in the gaseous form. The activity is therefore due to something inherent in the molecule. Optical activity of this kind was first noted in 1815 with a solution of sugar (Biot). Subsequently a number of optically active organic compounds were noted. Considerable confusion was caused by the cases of optical isomerism which were unearthed. For example, lactic acid was found in sour milk in 1780 by Scheele. In 1807 Berzelius isolated from muscle tissue a substance which was later shown to have the same formula and the same chemical reactions. Yet these substances, though both entitled to the name lactic acid, were not entirely the same, for

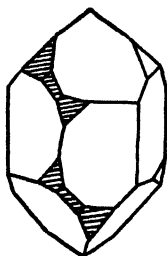


FIG. 49.

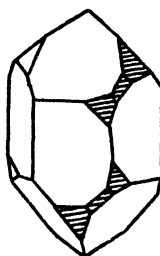


FIG. 50.

FIGS. 49, 50.—*d* and *l* quartz enantiomorphs (mirror-image crystals).

the milk acid was optically inactive, while the flesh acid (sarcolactic acid) was dextrorotatory. Later a third acid, this time levorotatory, was found. There was at the time no way of clearing up the difficulty, though it was recognized that the space arrangement of the atoms would be an important part of any adequate explanation (1869, Wislicenus).

"If it is once granted that molecules can be structurally identical and yet possess dissimilar properties, it can only be explained on the ground that the difference is due to a different arrangement of their atoms in space" (1873, Wislicenus).

At a somewhat earlier time than the date above, chemists were under the same difficulty with tartaric acid and racemic acid. Both have the same formula, but the former was dextrorotatory while the latter was inactive (*i*). Pasteur investigated sodium ammonium tartrate crystals in the light of Herschel's statement about the hemihedral facets of quartz. Supposing that the facets cause optical activity, there should be none on the racemic crystals, since the salt is inactive.

Pasteur found that the hemihedral facets were present, but noted that with the tartrate, as with quartz, they are differently placed on different crystals. He had the inspiration to pick out and separate the two enantiomorphous kinds of crystals. From one kind there was obtained the familiar *d*-tartaric acid, while the other yielded a new *l*-tartaric acid. When

they were mixed in equal proportions inactive racemic acid was obtained (1848).

Pasteur noted that while the hemihedral facets are present in solid quartz and tartaric acid, the former is optically active only in the solid state. The latter also shows optical activity in solution, hence the effect is not caused by the facets but evidently concerns the molecules. "Are the atoms of right-handed tartaric acid arranged along the spiral of a right-handed screw or . . . at the corners of an irregular tetrahedron . . . ? We cannot answer these questions."

### VAN'T HOFF-LE BEL THEORY

The answer was given almost simultaneously in 1874 by van't Hoff (Dutch) and Le Bel (French). It is most easily understood by the use of the molecular models.\* In Fig. 51 below, balls of different colors are shown at the corners of the tetrahedron (white, yellow, scarlet). Two are alike, and as a result, only the one arrangement shown is possible. Changing the colors from corner to corner will not alter the figure. It is a symmetrical model, having a plane of symmetry which passes through W and Y and midway between S and S.

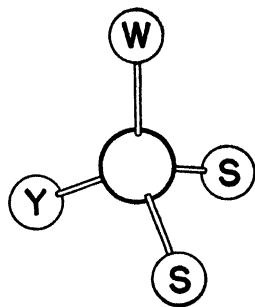


FIG. 51.—Symmetrical molecule.

If we make a model which has balls of *four different colors*, we can find no such plane of symmetry which will divide the model into equal halves. It is truly unsymmetrical, and as a result there are two different possible arrangements, and only two, which correspond to the right- and left-handed quartz crystals mentioned before.

These models are related to each other as the right hand is to the left. They have similar units but are not identical. One may not be superposed upon the other. If one model is held before a mirror, the image in the mirror corresponds to the arrangement of the other model (see Fig. 52).

The demonstration with the model can be applied directly to methane, if we imagine the colored balls to be atoms or groups introduced into the molecule by substitution.

**Asymmetric Carbon Atom.** It follows that a carbon atom with four different atoms or groups attached to it forms an asymmetric group, and that two different arrangements of the molecule can exist. Such a carbon atom is called an *asymmetric carbon atom*. The two compounds whose molecules are mirror images of each other are called **optical antipodes** or **enantiomorphs**. Van't Hoff and Le Bel stated that this asymmetry was the cause

\* The Kekulé and von Baeyer or other commercial models will be used in the classroom, but the student can make his own models by cutting corks and coloring the four apices with crayons or inks of different colors.

of optical activity, that every optically active compound must possess asymmetric carbon atoms, one or more.\* Several examples follow.

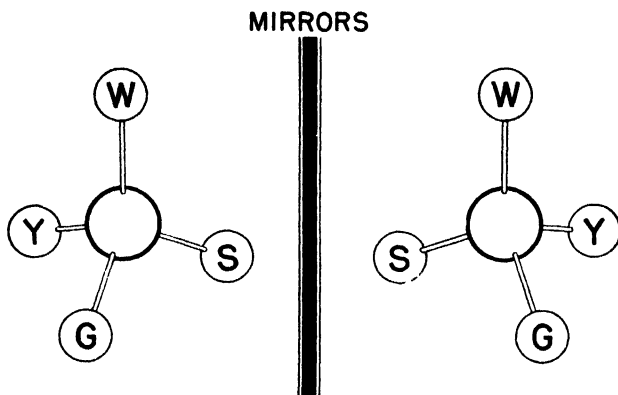


FIG. 52.—Models of optical enantiomorphs. The image of either in the mirror shows the configuration of the opposite model.

**Compounds with One Asymmetric Carbon Atom. Lactic Acid.** In lactic acid we have an unsymmetrical arrangement as previously discussed. The central carbon atom holds four different groups: namely H, OH, CH<sub>3</sub>, and CO<sub>2</sub>H. Thus two different space arrangements can be made, (I) and (II) below:

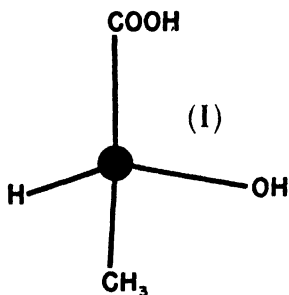


FIG. 53.

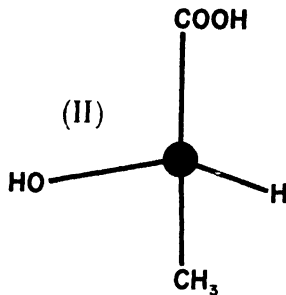


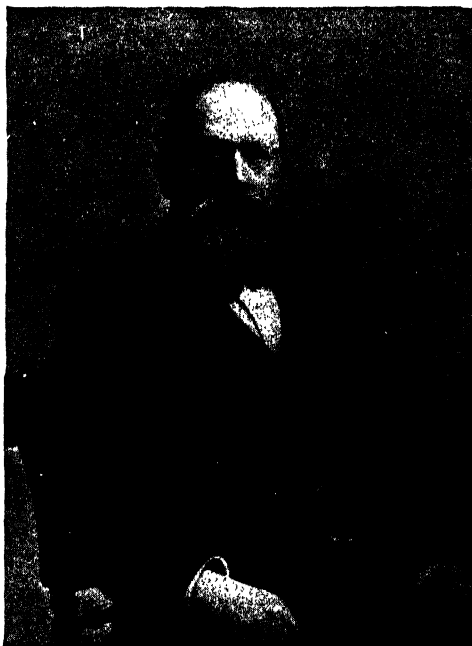
FIG. 54.

FIGS. 53, 54.—Lactic acids.

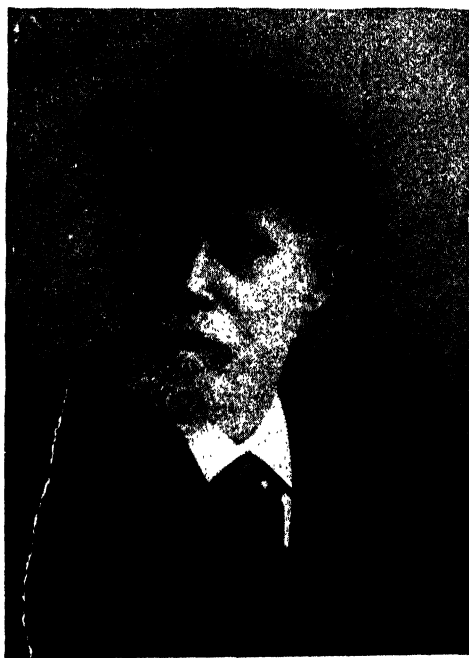
One of these is the structure for dextrorotatory lactic acid (we do not know which one) and the other is levorotatory lactic acid. As the compounds have the same groups and the same valency forces, it is not surprising that they should show identical physical properties. Nor is it surprising that the chemical properties should also agree. It is only when such

\* Optical activity is not of necessity associated with carbon atoms. Optically active compounds are known in which the central atom is N, S, P, Sn, etc. In every case the activity arises from molecular asymmetry as explained above. Quite naturally the carbon compounds have chief interest and importance.

CARL VON GRAEBE. (1841-1927, German.) He established the structure of alizarin and synthesized it (with Liebermann). He was associated with Bunsen and Baeyer, working for the latter four years as lecture assistant. He verified the Erlenmeyer formula for naphthalene and did much important synthetic work (quinones, rosolic acid, auramine, etc.). See *J. Chem. Education*, **7**, 2609 (1930).



*Berichte*, **61**, 9 (1928).



*Berichte*, **45**, 3597 (1912).

ALBERT LADENBURG. (1842-1911, German.) He was associated with Bunsen, Friedel, and Kekulé. He proved the equivalence of the hydrogens of benzene. He is known for his work in the alkaloid field and for his benzene formula as well as for extensive literary work. See *Am. Chem. J.*, **46**, 528 (1911), *J. Chem. Soc. (London)*, **103**, 1871 (1913).

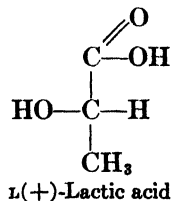
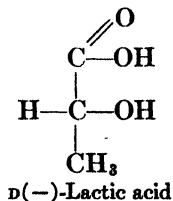
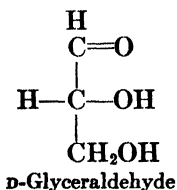
molecules react with other optically active compounds, such as are found in the cells of our bodies, that differences are seen between the two compounds.

If equal amounts of *d*- and *l*-lactic acids are mixed, the rotational effect of one-half of the molecules is cancelled by that of the other half; the mixture is inactive. Such mixtures are called *racemic mixtures*. Means have been found for separating them into their *d*- and *l*-components.

**Projection Formulas of Lactic Acids.** It is desirable to use graphic formulas for the representation of optically active compounds rather than sketches of models, and if certain conventions are adopted this can be done. Lactic acid is written with the carboxyl group at the top of the formula and methyl group at the bottom.

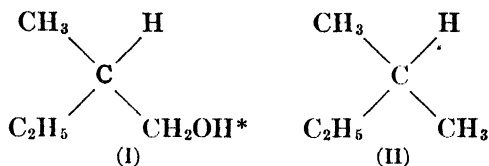
The position of the hydroxyl group is determined by the relationship of the lactic acids to dextrorotatory glyceraldehyde, which is taken as a reference standard. The formula for *d*-glyceraldehyde is by convention written with the hydroxyl group at the right hand; hence levorotatory lactic acid which is related to this glyceraldehyde has its hydroxyl group also at the right.

The structural relationship between molecules is considered as more important than the direction of optical rotation. Actually the rotation may change markedly for very little apparent cause. For example, all salts of the dextrorotatory lactic acid are levorotatory. In the names of the following formulas the small capital letters show the structural relationship to glyceraldehyde just discussed, and the plus and minus signs indicate actual optical rotation.



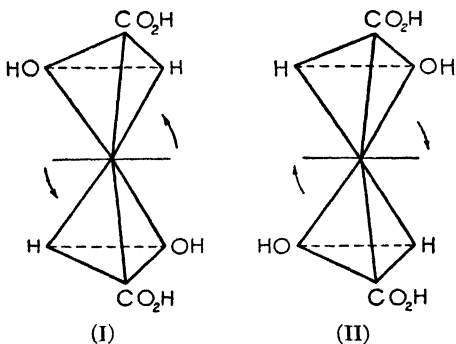
**Dependence of Optical Activity upon Asymmetry.** The crux of the theory presented here is that optical activity rests upon molecular asymmetry.\* The theory has been completely successful in the face of thousands of tests. The following tests illustrate the point. 2-Methyl-1-butanol (I) is active. It is easy to make various derivatives by modification of the OH group (chloride, bromide, ether, ester, etc.), or the CH<sub>2</sub>OH group (aldehyde, acid). All are active.

\* Thus there are cases where molecules are asymmetric (and optically active) which do not possess asymmetric carbon atoms. We will, however, limit ourselves to simple cases in which asymmetry is linked with asymmetric carbon atoms (see page 421).



When, however, we reduce the  $\text{CH}_2\text{OH}$  group to  $\text{CH}_3$ , activity disappears (II) along with molecular asymmetry. The theory is a practical one. It links optical activity with molecular structure, but does not say why asymmetrical molecules affect polarized light as they do. This is still a subject for research.

**Compounds with More than One Asymmetric Carbon Atom.** We may use tartaric acid as an example. Here we have two asymmetric carbon atoms, each holding H, OH,  $\text{CO}_2\text{H}$ , and the group C(a, b, c) on the four available valences.



FIGS. 55, 56.—D(−)- and L(+)-Tartaric acids.

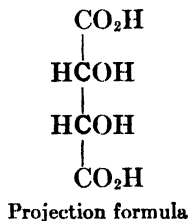
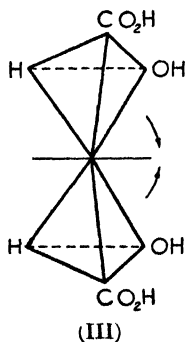
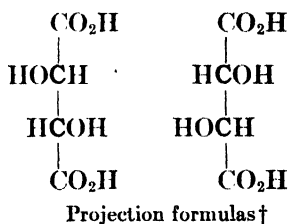


FIG. 57.—Mesotartaric acid.

\* Carbon atoms printed in heavy type are asymmetric.

† The hydroxyl group on the asymmetric carbon most remote from the top carboxyl determines the family to which the compound belongs. If this hydroxyl group extends to the right the compound is called D- and vice versa.



If we assume that in (I) the upper carbon atom is levorotatory it is evident that the lower carbon atom is also, since the H, OH, and CO<sub>2</sub>H groups are in the same relative order in each half of the molecule. One can easily see this by imagining the lower group to rotate through an angle of 180° while staying in the plane of the paper. This would then represent *l*-tartaric acid. As (II) is the mirror image of (I), this would be *d*-tartaric acid.

Again, we see that the optical activities of the upper and lower carbon atoms are equal, because of the equality of the groups attached to them. This makes possible another arrangement (III), in which the *d*-rotation of the upper carbon atom is exactly cancelled by the *l*-rotation of the lower carbon. This represents a third tartaric acid, known as inactive or meso-tartaric acid. As said before, the *d*- and *l*-acids are alike in physical properties and practically all of their chemical properties. The *meso* acid is not a mirror image of either of the others however, and has different physical properties.

**External and Internal Compensation** If equal amounts of *d*- and *l*-tartaric acid are mixed in a solvent, the solution is inactive as would be expected. Such inactivity is said to be due to "external compensation" and there are ways of separating such racemic mixtures. With mesotartaric acid the

TABLE 29.—PHYSICAL PROPERTIES OF TARTARIC ACIDS

Name	M.p.	Sp. g., 20°/4°	Solubility in water, g./100 cc.
L(+)-Tartaric acid . . . . .	168–70°	1.760	139
D(–)-Tartaric acid . . . . .	168–70	1.760	139
Meso acid . . . . .	140	1.666	120
Racemic acid . . . . .	205–6	1.697	20.6

inactivity is due to effects within the molecule (not external). This inactivity, due to "internal compensation," is permanent. It will be found in all compounds of two or more asymmetric carbon atoms which have a plane or point of symmetry. The plane of symmetry is shown in (III) by the horizontal line.

**Racemic Acid.** Evaporation of a racemic mixture of tartaric acids gives a new substance whose physical properties are different from those of *d*- or *l*-tartaric acid. Its melting point is higher, it has a different water solubility and crystallizes with one molecule of water (the *d*- and *l*-acids are anhydrous). This is apparently a loose compound, somewhat like a double-salt, of the *d*- and *l*-acids. It is called racemic acid. Other cases of this kind are known in which *dl* mixtures yield a *dl* solid having individual physical properties. Upon solution such *racemic compounds* revert to simple racemic mixtures.

**Number of Optical Isomers.** Theoretically the number of optical isomers possible, exclusive of racemates, is  $2^n$ ,  $n$  being the number of asymmetric carbon atoms present. This is the **van't Hoff rule**. According to it there should be four tartaric acids, since there are two asymmetric carbon atoms in the compound. The number is reduced to three, because one of the forms has a plane of symmetry and hence is inactive. Because of such possible exceptions every new case must be worked out individually. Van't Hoff's rule gives the maximum number of isomers possible under any conditions, but the actual number may be smaller.

### RESOLUTION OF RACEMIC MIXTURES

The separation of a racemic mixture into its *d*- and *l*-components is termed its resolution. Several methods are available; those which follow were originally devised by Pasteur.

(a) *Mechanical Separation.* When the substance forms well defined crystals, the *d*- and *l*-forms, being mirror images of each other, may be picked apart by hand. This method has historical interest because it was employed by Pasteur for the separation of the tartaric acids. It does not often happen that *d*- and *l*-compounds crystallize in the manner suggested; even if this were the rule the method would still be extremely slow. In the case of the sodium ammonium tartrates with which Pasteur worked, the enantiomorphic crystals separate only at temperatures below 28°. Above this transition temperature the sodium ammonium racemate separates. This explains why Pasteur obtained a different result from that obtained by others. In his experiment the temperature happened to be favorable. In this case, as in many others, "chance favored the right man."

(b) *Biochemical Method.* A culture of a mold, bacterium, or yeast is allowed to grow in the racemic mixture. Without doubt the organism contains an optically active compound or compounds which react with one of the optical antipodes and not the other; at any rate one is destroyed. For example, if the mold *Penicillium glaucum* is grown in a solution of ammonium racemate (fortified with nutrient salts) the solution becomes *l*-rotatory due to the destruction of the *d*-tartrate by chemical action in some way induced by the mold.

The method has obvious disadvantages in that 50% of the active material is lost and that the yield of remaining material may be low. The method may be useful in finding whether an inactive solution is a racemic mixture or a solution of a *meso* compound (inactive by internal compensation).

(c) *Resolution by Use of Active Compounds.* This is the method most often used. Depending upon the chemical nature of the active compound in hand, a derivative is made with another active compound, often a natural compound. Thus an active base (alkaloid) such as *l*-morphine, *l*-quinine, or *l*-brucine could be used to form a salt in case a *dl* mixture of acid was to be

resolved. The two salts formed would not be enantiomorphs for (supposing the base to be levorotatory) they would be constituted as follows:



It is seen that these are not mirror images of each other. Hence the salts have different properties and they are usually separated by fractional crystallization, which takes advantage of their differing solubilities in solvents. The pure *d*- and *l*-acids are later obtained by ordinary chemical methods from the separated salts, I and II. Compounds like I and II which are stereoisomers but not enantiomorphs are called **diastereoisomers**.

A racemic mixture of a base can be resolved by reversing this process, i.e., by using an active acid, such as *d*-tartaric. A *dl* alcohol mixture may be esterified with an active acid. Or the alcohol may be esterified with one

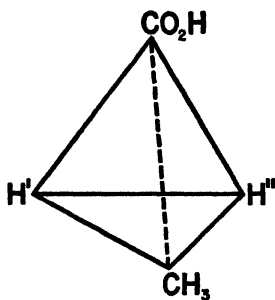


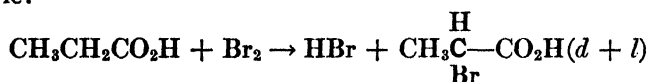
FIG. 58.—Propionic acid.

carboxyl of a dicarboxylic acid like succinic acid, then the other carboxyl used to form a salt with an active base. Many ingenious schemes have been devised to make derivatives such as the above to be used for resolutions.

**Racemization.** It is frequently observed that an active substance becomes optically inactive, sometimes upon standing, but more often when it is heated. In other cases the change occurs in the presence of a base or traces of various compounds which act as catalysts for the change.

Half of the active material changes to the isomer of opposite rotation, giving a racemic mixture. Thus when cinchonine-*d*-tartrate is heated to 170°, racemic acid and mesotartaric acid form (Pasteur). In performing resolutions by the chemical method there is always the possibility that racemization may occur and thus undo the work.

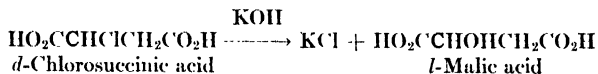
**Asymmetric Synthesis.** When in synthetic work we perform a reaction that transforms an optically inactive compound to an active compound, it is noted that we obtain a racemic mixture. Thus the bromination of propionic acid (inactive) gives  $\alpha$ -bromopropionic acid, in which the *alpha* carbon is asymmetric:



It is easy to see why this must be so. The two *alpha* hydrogens of propionic acid are held with equal force in a molecule which has a plane of symmetry, therefore hydrogen 1 may as easily be replaced as hydrogen 2 (see Fig. 58). According to the law of chance we secure equal amounts of the *d*- and *l*-bromoacids.

If, however, we begin operations with an asymmetric molecule, and add an asymmetric carbon atom, it is possible that the synthesis might not give equal amounts of the new optical isomers. Cases of this kind have been observed in the laboratory (see page 358). In nature the occurrence is common.

**Walden Inversion.** When an atom or group *directly connected to an asymmetric carbon atom* is replaced, the configuration of the new compound may be opposite that of the original. Thus *d*-chlorosuccinic acid, upon treatment with potassium hydroxide, gives *l*-malic acid:



When *d*-chlorosuccinic acid is treated with silver oxide we get *d*-malic acid. It is evident that in one of these substitutions there has been a change of configuration about the asymmetric carbon atom.

A change of this kind is known as a Walden inversion. Though much work has been carried out with this reaction the mechanism is not yet known.

### IMPORTANCE OF OPTICAL ACTIVITY

A large majority of the natural compounds which are desirable for medical uses are optically active. One might mention alkaloids, hormones, vitamins. Frequently only one form, *d* or *l*, is found in nature. There is a more and more insistent demand that these compounds be made synthetically, in order to have an assured source of compounds of known high purity. Very often the optical isomers of such compounds have very different physiological effects. Thus the natural *l*-adrenaline is about twelve times as active as *d*-adrenaline. *l*-Hyoscyamine is effective, but *d*-hyoscyamine appears to have little or no physiological effect.

The chemist must, therefore, be able to separate the racemic mixtures which result upon synthesis of such compounds, in order to deliver the active *d*- or *l*-isomer to his co-workers in medicine.

### REVIEW QUESTIONS

1. Why is it that the physical properties of geometrical isomers differ while those of optical *d*- and *l*-isomers are the same?
2. Why do we expect optical isomers to be alike in their chemistry? Illustrate by the use of models or projection formulas.
3. Is it reasonable that geometrical isomers should have like chemical properties? Why? Use models or projection formulas in your explanation.
4. How could the biochemical method of separation be used to determine whether a certain solution was a racemic mixture?
5. Write graphic formulas for the isomers of formula  $\text{C}_6\text{H}_{11}\text{N}$ . Indicate which are optically active. State the total number of isomers, exclusive of racemates.
6. Oxidation of maleic acid gives mesotartaric acid, while a similar oxidation of fumaric acid gives a racemic mixture of *d*- and *l*-tartaric acids. Explain these facts (it may be necessary to use the molecular models).
7. Which of the following are optically active compounds? (a) 2-Hydroxybutane; (b) 3-Hydroxypentane; (c)  $\alpha$ -Chlorobutyric acid; (d) 2,2-Dichloropropane; (e) 1,2-Epoxypro-

pane. Write the graphic formula of each and indicate asymmetric carbon atoms by the use of a star.

8. Inspect the following formulas and encircle any carbon atoms which are asymmetric.  
(a)  $\text{CH}_3\text{CHOHCHOHCOOC}_2\text{H}_5$ ; (b)  $\text{C}_2\text{H}_5\text{NHCH}(\text{CH}_3)_2$ ; (c)  $\text{ClCH}_2\text{CHClCHCl}_2$ ; (d)  $\text{CH}_3\text{OCH}(\text{CH}_3)(\text{C}_2\text{H}_5)$ ; (e)  $\text{CH}_3\text{CHClCOOH}$ .
9. Discuss the methods used to separate a racemic mixture into its *d*- and *l*- components.
10. Define and discuss: Racemization; Asymmetric synthesis.
11. Define the following terms: (a) Isomerism; (b) Geometrical isomerism; (c) Structural isomerism; (d) Optical isomerism; (e) Metamerism; (f) Tautomerism.
12. Wherein do the properties of *cis* and *trans* isomers differ? Wherein do those of optical isomers differ?
13. How does the optical activity of quartz differ profoundly from that of camphor?
14. Nature makes *d*-camphor. In our laboratory synthesis we get a mixture of 50% *d*-, 50% *l*-camphor. Explain.
15. What is meant by the following terms? (a) Optical activity; (b) Asymmetric carbon atom; (c) Specific rotation.
16. Explain with the use of diagrams the meaning of the expressions, "Compound inactive by internal compensation," and "Mixture inactive by external compensation."
17. Write the formula of a compound having 4 carbon, 2 oxygen, 4 chlorine, and 6 hydrogen atoms, which is optically inactive. Write a formula for an isomer of this compound which has but two asymmetric carbon atoms.
18. Can you explain why the optical isomers of a compound used in medicine have such different physiological responses?
19. (a) Write graphic formulas for lactic aldehyde representing each form of the compound. (b) Write graphic formulas for the new compounds formed by addition of  $\text{HCN}$  to lactic aldehyde. (c) How many different acids would result upon hydrolysis of the cyanohydrins of (b)? (d) Are any of the acids in the *meso* form?
20. Which of the amyl alcohols are optically active? Write their graphic formulas. Indicate clearly the number of asymmetric carbon atoms in each active compound.
21. A ketone having five carbon atoms yields an oxime whose reduction produces an amine with one asymmetric carbon atom. Write the graphic formulas for possible structures of the original ketone, and for one structure which is ruled out by the conditions imposed.

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## CARBOHYDRATES

**Introduction.** The three great classes of foodstuffs utilized by man and the animals are the fats, the proteins, and the carbohydrates. Of these the latter have as well an industrial importance, which perhaps exceeds that of either proteins or fats. The carbohydrates are C, H, O compounds, mainly of vegetable origin; a large percentage (about 75%) of the solid material of the plants is composed of these substances.

The class name "carbohydrate" designates these compounds as hydrates of carbon; the formulas of many of the members suggest such a classification, because they contain H and O in the proportion of 2 to 1, as in water. Thus  $C_6H_{12}O_6$  may be written  $C_6(H_2O)_6$ ,  $C_{12}H_{22}O_{11}$  as  $C_{12}(H_2O)_{11}$ , etc. Moreover, it is true that cane sugar and certain other carbohydrates, when treated with concentrated sulfuric acid or strongly heated, will decompose, leaving behind a residue of carbon.

However many substances exist which, on the simple basis of their formulas, should belong among the carbohydrates; for instance formaldehyde, which may be written  $CH_2O$ , or acetic acid,  $C_2(H_2O)_2$ , or lactic acid,  $C_3(H_2O)_3$ . We know that these compounds are not of the carbohydrate series, while at the same time other substances which are unmistakably carbohydrates have formulas that would not entitle them to the name (an example is rhamnose,  $C_6H_{12}O_5$ ). The early conception is therefore abandoned. We might define carbohydrates as ketone-polyalcohols or aldehyde-polyalcohols, or substances which upon hydrolysis will yield the above (either or both). However, some compounds answering this description are not carbohydrates. It is difficult to give a rigid definition. Many but by no means all carbohydrates have the empirical formula  $C_n(H_2O)_m$ .

## CLASSIFICATION OF CARBOHYDRATES. NOMENCLATURE

Carbohydrates are divided into classes according to their behavior with hydrolytic agents. The simplest carbohydrates, called monosaccharides, do not hydrolyze; a disaccharide molecule hydrolyzes to yield two molecules of monosaccharide (which may be identical or different). A trisaccharide upon hydrolysis gives three monosaccharide molecules.

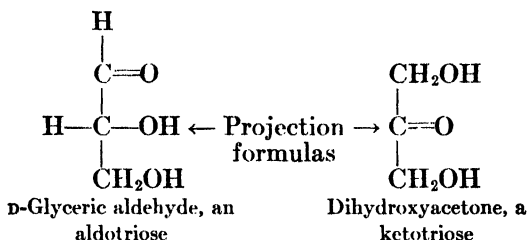
The mono- and disaccharides are sweet, crystalline, water-soluble substances called *sugars*. Sugars are less soluble in alcohol than in water, and are practically insoluble in ether and non-polar organic solvents. All natural sugars are optically active.

Saccharides which yield more than two monosaccharides upon hydrolysis are called *polysaccharides*.\* The complex polysaccharides include the starches, cellulose, and the dextrins; non-crystalline substances, for the most part insoluble in water and tasteless. The two grand divisions of the carbohydrates are thus the sugars and the non-sugars (starches, cellulose, etc.).

The monosaccharides are further divided into the "oses," according to the number of carbon atoms in the molecule, thus: a diose has two carbons, a triose has three, etc. Representatives are known of all classes up to and including  $C_{10}$  (decoses).

The pentoses and hexoses are the most important of the monosaccharides; trioses and tetroses have merely a theoretical interest. Monosaccharides which are aldehyde-alcohols are called **aldoses**; keto-alcohol monosaccharides are called **ketoses**. By combining these terms we get class names such as aldopentose (aldehyde sugar with five carbons), ketotetrose (ketonic sugar with four carbons).

Examples.



The above are the simplest representatives of their respective classes.

**Derivation of Formulas.** The simplest hydroxyaldehyde is glycolic aldehyde,  $\text{HOCH}_2\text{CHO}$ , and while this reacts like a simple sugar, we have given glyceric aldehyde above as the simplest aldose, because it, like all natural sugars, is optically active. By adding  $\text{CHOH}$  groups to glyceric aldehyde two whole families or series of aldoses can be constructed. Those derived from *D*-glyceric aldehyde belong to the *D*-family, those from *L*-glyceric aldehyde to the *L*-family. This classification has nothing to do with the actual sign of optical rotation of any of these sugars, but is purely conventional.

The projection formula of an aldose is usually written with aldehyde group at the top and primary alcohol group at the bottom. The carbon atoms are numbered consecutively, the aldehyde carbon being #1. The formula for a ketose is written so as to give the carbonyl group the lowest possible number, the upper carbon of the chain being #1.

Using these conventions a substance of the *D*-series has the  $\text{OH}$  group of the highest-numbered asymmetric carbon atom at the right side of the chain. A substance of the *L*-series has this  $\text{OH}$  group at the left side of the chain (see formulas, page 346).

\* Di-, tri-, and tetrasaccharides of known constitution are known as **oligosaccharides**.

*Formulas of D-Glyceraldehyde.* Using a tetrahedron for the central carbon atom gives (I) below. Another type of formula (II) uses a dash line with vertical stroke for the OH group; the H is to be imagined opposite this line and the asymmetric carbon atom is not shown. The formula may also be written as in (III) with a plus sign to show that OH is at the right side. Again the asymmetric carbon is omitted.

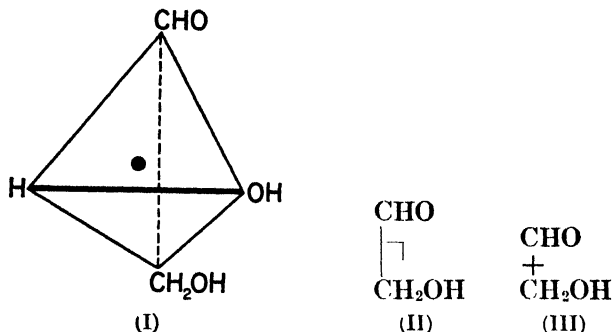


FIG. 59.—Formulas for a D-aldotriose.

A formulation based on (III) is conveniently used to designate sugars. In this formulation D-glucose is symbolized as in (I) below, D-mannose as in (II). The aldehyde and primary alcohol groups are omitted and the plus and minus signs indicate HCOH and HOCH groups. Carbon #1 is at the right hand.



If a sugar belongs to the D-family but is actually levorotatory, it may be written D(−) to indicate this fact. Example, D(−)-fructose. Similarly a sugar of the L-family which is dextrorotatory will be written L(+).\*

The projection formulas for the D-series of aldoses through the hexoses are given on p. 346. Each new asymmetric carbon atom introduces two new optical isomers, thus there are two tetroses, four pentoses, etc. In comparing such formulas they may be rotated in the plane of the paper; they must not be removed from the plane of the paper.

**Epimers.** Sugars which are isomeric and which are alike in all respects except for the H and OH arrangement on carbon atom #2, are called epimers. Thus xylose and lyxose are epimeric, as are erythrose and threose.

### MONOSACCHARIDES OR MONOSES

As previously stated, the pentoses and hexoses are the most important groups contained in the class of monosaccharides. A few will be described individually.

\* In some books and journal articles the notation *d'* is used for D(−) and *l'* for L(+). *Italic large capitals* are sometimes used rather than plain small capitals.



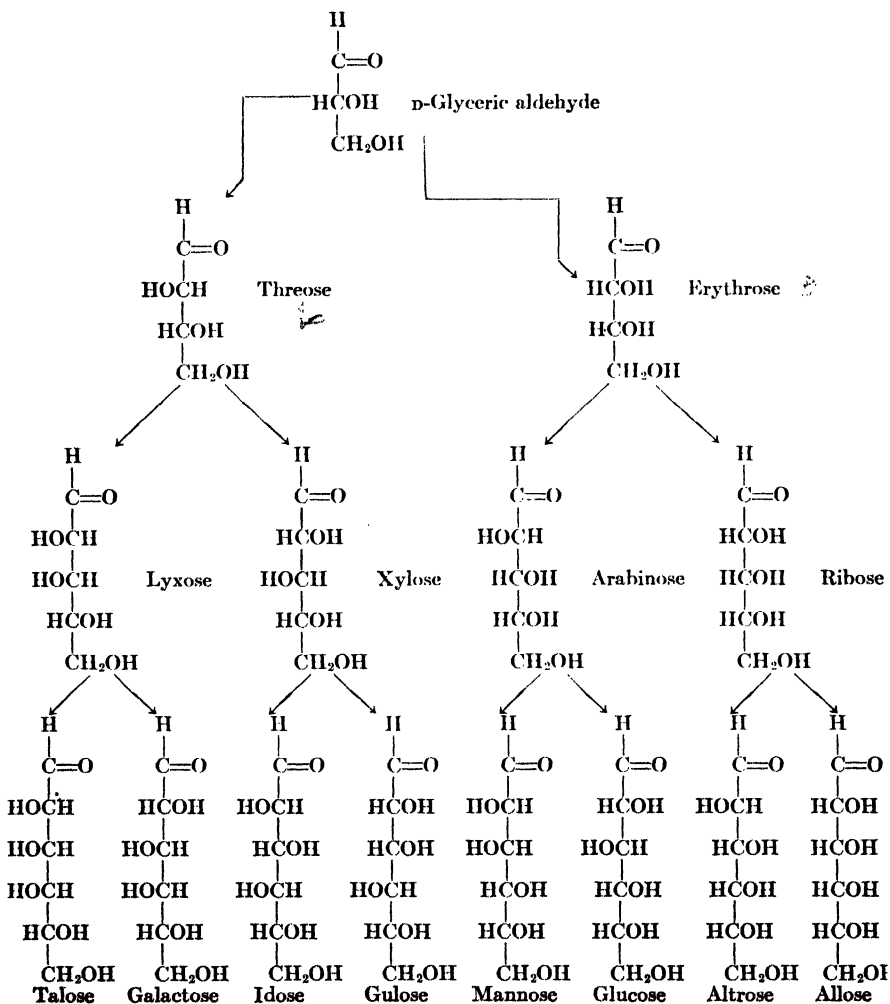
## PENTOSES

The formula for a pentose is  $C_5H_{10}O_5$ ; these compounds are well distributed in nature as constituents of complex molecules called pentosans.\* They result from the hydrolysis of the pentosans.

H

**L-Arabinose**, an aldopentose,  $CH_2OH(CHOH)_3C=O$ , is obtained from gum arabic by boiling with dilute sulfuric acid. Another source is wood or bran. **D-Arabinose** is obtained on hydrolysis of certain glycosides.

## PROJECTION FORMULAS OF D-ALDOSES



\* Pentose molecules lose water cooperatively to form "anhydrides" called pentosans. Hexoses similarly give hexosans. A derivative formed in this way from glucose (dextrose) is a dextran, one made from xylose is a xylosan, (xylan), etc.

**D-Xylose** may be had from straw or corn cobs by acid hydrolysis. Pentoses differ from hexoses in that yeast does not cause their fermentation. They easily form furfural when boiled with hydrochloric acid. The presence of furfural may be detected by holding a paper moistened with aniline acetate solution in the escaping vapor. A red color is produced.

Xylose is a starting material for the synthesis of Vitamin C (page 751).

## HEXOSES

Glucose and fructose are the only hexoses which occur free in nature. In fact they are the only monosaccharides found free in large amounts. Hexoses, including these two, also occur in combination in the disaccharides in glycosides, and in polysaccharides.

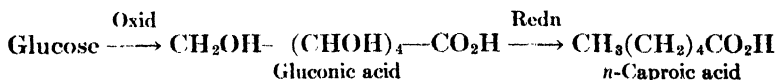
**D-Glucose.** The formula for the hexoses is  $C_6H_{12}O_6$ . Within this class glucose (dextrose)\* is the most important compound. It is found in honey, in the juices of many fruits, and in grapes, hence the name grape sugar which has been applied to this compound. Several disaccharides upon hydrolysis yield glucose, as will be noted in a later section. The blood normally contains about 0.1% of glucose; in diabetes the amount is largely increased. Small amounts are normally carried in the urine. Glucose is the only sugar obtained in complete hydrolysis of cellulose, starches, and maltose. It is the sugar usually produced upon hydrolysis of the natural glycosides (hence the class name). Glucose is used as a sweetening agent in chewing gum, table syrups, other food products; it is employed in making candy and jellies, in pharmaceutical preparations. As a reducing agent glucose is used in silvering solutions and to change indigo to indigo-white. Commercially glucose is prepared by the hydrolysis of starch (page 379).

**Structural Formula for Glucose.** The structural formula for glucose is  $CH_2OH(CHOH)_4CHO$ . It will be to our interest to examine briefly the steps which have led to the adoption of this formula. The molecular formula of glucose,  $C_6H_{12}O_6$ , is of course obtained as the result of quantitative analysis of the compound and determination of its molecular weight (page 10, ff.).

(a) The partial reduction of glucose yields sorbitol, a polyhydroxy alcohol whose structure is known:



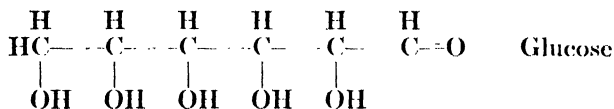
therefore the carbon chain of glucose is a straight chain of six carbons, as we know it to be in sorbitol. This evidence is confirmed by the fact that complete reduction of glucose produces derivatives of normal hexane. A somewhat better method of proof is the following: oxidation of glucose gives gluconic acid, and reduction of gluconic acid gives *n*-caproic acid.



\* The name arises from the fact that glucose is dextrorotatory.

(b) Various characteristic tests show that glucose has an aldehyde group (see next section). Careful oxidation gives gluconic acid shown above. This is a monocarboxylic acid, thus there is but one aldehyde group in the molecule of glucose. As CHO group is monovalent\* it must always be on the end of the chain. Further oxidation yields the dicarboxylic acid, saccharic acid,  $\text{CO}_2\text{H}-(\text{CHOH})_4-\text{CO}_2\text{H}$ .

(c) Treatment with acetic anhydride introduces five acetyl groups; hence there are five OH groups in glucose. The formula thus becomes:



The OH groups in glucose are assigned one to each carbon atom, because they are so placed in sorbitol, reduction product of glucose, and because experience has revealed but few compounds with two OH groups on one carbon. Such carbons generally display aldehyde or ketone reactions. Since there are 4 asymmetric carbon atoms in the formula it is evident that it represents 16 different optical isomers (see van't Hoff rule, page 339). One of these formulas belongs to ordinary glucose (see page 359). All of these 16 aldohexoses have now been made.

The position in space occupied by the H and OH groups of glucose is not indicated in this structural formula, but appears in the graphic formulas on pages 358, 361. The ring forms which glucose can assume will be discussed later.

#### CHEMICAL REACTIONS OF GLUCOSE

*Glucose shows the possession of an aldehyde group by the following reactions:*

(a) It adds hydrogen cyanide, condenses with hydroxylamine to form an oxime, and with phenylhydrazine to give a phenylhydrazone. It does *not* color Schiff reagent or add sodium bisulfite.†

(b) Glucose is easily oxidized by silver or copper ion. When ammoniacal silver nitrate solution is used, a silver mirror is formed. With Fehling's solution a precipitate of cuprous oxide is produced.

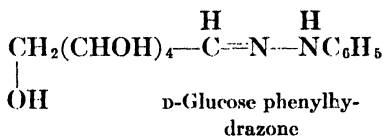
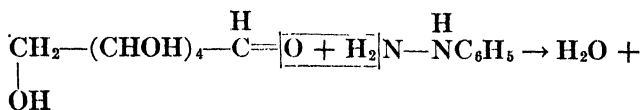
(c) Glucose when boiled with strong alkali gives a resinous product.

All of the positive reactions cited here will be recognized as typical of the aldehyde group.

*Reactions of Glucose with Phenylhydrazine.* Glucose reacts with phenylhydrazine in the normal way to form glucose phenylhydrazone:

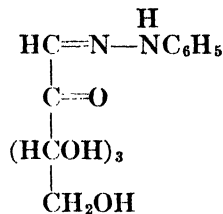
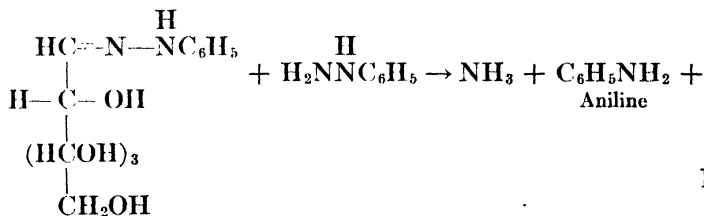
\* See footnote, page 15.

† See *Ind. Eng. Chem. (Anal.)* 14, 405 (1942) for description of a supersensitive Schiff reagent which may be used with carbohydrates.

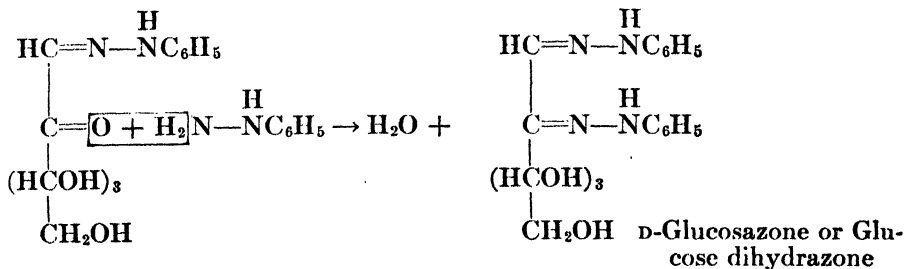


The phenylhydrazone of glucose, like those of most of the hexoses, is soluble in water and does not precipitate when the above reaction is carried out. The osazone, described next, is more easily prepared.

If glucose is treated with an excess of phenylhydrazine, the phenylhydrazone is formed, and the excess reagent then *acts as an oxidizing agent*, attacking the carbon atom at position #2 and oxidizing it from secondary alcohol to ketone:



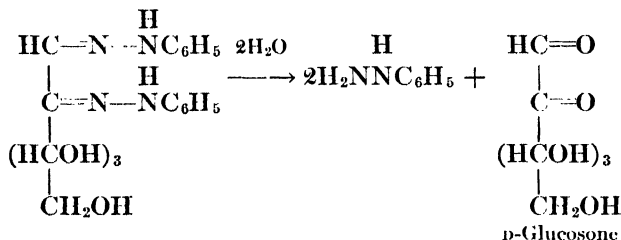
The molecule of phenylhydrazine which performs the oxidation is itself reduced to aniline and ammonia, as shown in the equation. A third molecule of reagent now unites with the newly created carbonyl group:



The product of the reaction of excess phenylhydrazine with a hexose is called in general an *osazone*—in this case *glucosazone*. Osazones are very useful in the identification of sugars, as they are insoluble in water, and are solids with definite melting points; also under the microscope they show definite and characteristic crystal form.

It has been noted that when definite concentrations of reagents are used, the osazones of different sugars precipitate at different time intervals (Maquenne test). Thus the osazone of D-glucose precipitates suddenly in 4-5 minutes after mixing of the reagents, while the time for D-galactose is 15-19 minutes and for D-fructose is about 2 minutes. This test is often useful in identifications.

Upon hydrolysis an osazone yields a compound with both a ketone and an aldehyde group, called an *osone*—in this case *glucosone*:



Osones will be discussed in a later paragraph.

Natural hexoses are subject to fermentation in the presence of ferments or enzymes. The products when glucose is fermented by zymase are carbon dioxide and ethyl alcohol:



D(-)-**Fructose**,\* fruit sugar, levulose. Like glucose, fructose is very generally distributed in the plants. It is a hydrolysis product of various carbohydrates, being best obtained from inulin, a polysaccharide found in the dahlia, artichoke, etc., by treatment with dilute acid. The name levulose is often applied to fructose on account of its optical rotation, which is levorotatory. Yeast fermentation of fructose yields carbon dioxide and alcohol.

The structure of fructose is determined by inference from a series of chemical reactions similar to those employed in the case of glucose.

(a) Acetylation with acetic anhydride proves the presence of five OH groups in fructose.

(b) Partial reduction products of fructose are polyhydroxy alcohols with straight chains of six carbon atoms; therefore the molecule of fructose has also a normal six-carbon chain.

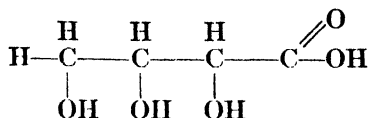
(c) The formation of a phenylhydrazone proves the presence of a carbonyl group, however:

(d) Fructose is not an aldehyde, because its oxidation does not yield an acid with a like number of carbon atoms. Instead two acids of lesser carbon content are formed. This is characteristic of ketones. Fructose is

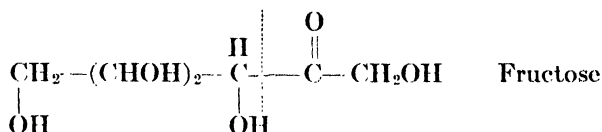
therefore a keto-alcohol. Glycolic acid,  $\text{HOC}-\overset{\text{H}}{\underset{\text{H}}{\text{C}}}=\overset{\text{O}}{\text{O}}$ , and trihydroxy-

butyric acid,

\* D-Fructose and other D-sugars are structurally related to D-glucose (ultimately to D-glyceraldehyde). Their optical rotations are not indicated by this initial letter. D-Fructose is levorotatory,  $[\alpha]_{\text{D}} = -92.3^\circ$ . The anomaly is shown by the use of the minus sign (see page 345).



are the acids which result from the oxidation of fructose with mercuric oxide. We already know that when a ketone is oxidized its carbon chain breaks next to the carbonyl group (page 153). Thus a knowledge of the oxidation products of fructose, together with the information given in the next section, enables us to construct its formula, which must be as follows:

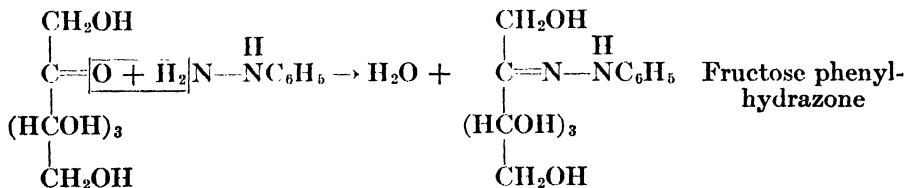


The dotted line shows where the break occurs on oxidation. The cyclic forms of fructose are shown on page 362.

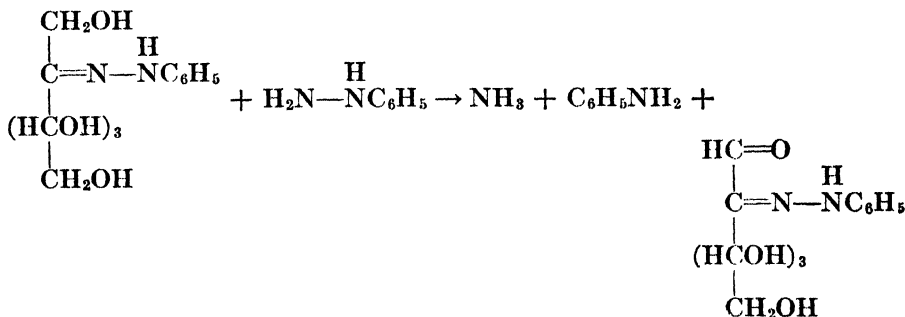
#### CHEMICAL REACTIONS OF FRUCTOSE

Fructose, unlike ordinary ketones, is oxidized by Fehling's solution. This is true of other  $\alpha$ -hydroxy ketones as well. Fructose reduces Fehling's solution even more rapidly than does glucose.

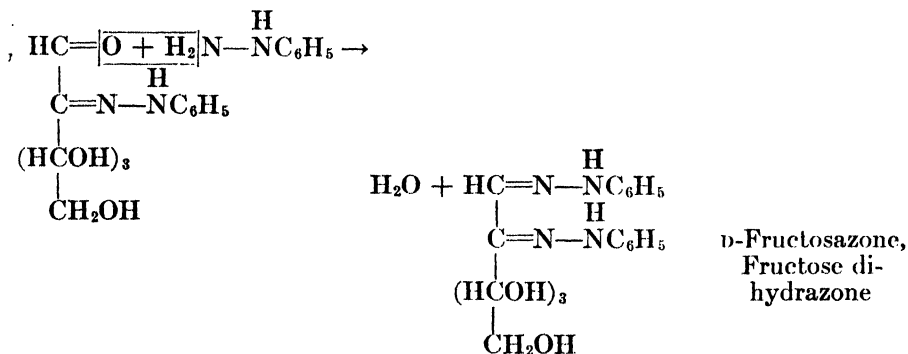
With phenylhydrazine a phenylhydrazone is formed as has already been stated:



An excess of the reagent acts on fructose phenylhydrazone, first as an oxidizing agent, converting the primary alcohol group at carbon #1 to an aldehyde:



The phenylhydrazine is by this action reduced to aniline and ammonia. Subsequently another molecule of the hydrazine reacts with the aldehyde group, forming an osazone:



The osazone formed from D-fructose has of course the same molecular formula as that formed from D-glucose (see page 349) and is *identical with it*. It must be emphasized that both D-glucose and D-fructose are optically active compounds, each having several asymmetric carbon atoms; the osazone is also active. Therefore if both yield one and the same osazone, this proves beyond a doubt that the disposition of OH and H about the last four carbon atoms in each molecule is the same for one as for the other. In other words, the only structural difference between D-glucose and D-fructose is to be found in the two carbons on the "active" end of the molecule. For this reason it is quite possible to convert glucose to fructose and vice versa by suitable reagents which will affect these two carbons. This will be illustrated later.

**D-Mannose.** Mannose occurs in the polysaccharides called mannans and certain of the glycosides. It is obtained from hydrolysis of the vegetable ivory nut (*tagud*). The ivory (*corajo*) is used for making buttons and the waste is used for making mannose. Mannose is the epimer of glucose. It ferments with yeast. Its reduction gives mannitol (page 111).

**D-Galactose.** This is best made by hydrolysis of lactose (milk sugar). In the body galactose is made in the mammary glands from glucose, then combined with glucose to form lactose. Galactose occurs in polyoses, in glycosides, and in cerebrosides (glycolipides), which are found in brain and nerve tissue. For ring formulas of mannose and galactose, see page 362.

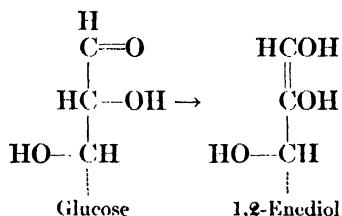
#### GENERAL REACTIONS OF MONOSACCHARIDES

Glucose and fructose have been treated in some detail. Other aldohexoses are similar to glucose. They form the same types of derivatives, show mutarotation (page 360), oxidize with Fehling's solution, etc. The following material constitutes a review and extension of that already given.

(1) *They oxidize with ease*, the aldoses to monocarboxylic and dicarboxylic acids of the same carbon content, the ketoses to acids with a smaller number of carbons. The lactones of the monocarboxylic acids may readily be reduced to aldehydes. Examples of these reactions are given elsewhere.

(2) *Oxidation yields various products according to conditions*. Bromine water gives gluconic acid from glucose and oxidizes other aldoses, but does not affect ketoses.\* Nitric acid oxidizes glucose to saccharic acid. This with potassium permanganate gives oxalic and tartaric acids. For oxidation of fructose see page 350. Oxidation of monosaccharides with nitric acid gives, finally, oxalic acid. Hot chromic acid gives  $\text{CO}_2$  and  $\text{H}_2\text{O}$ .

*Alkaline oxidation*. Glucose is stable in faintly acid solution but is very sensitive to alkali. If allowed to stand with very dilute alkali, enolization takes place. The 1,2-, 2,3-, and 3,4-enediols are formed:



One consequence of this is the Lobry de Bruyn transformation (page 358). In presence of atmospheric oxygen or stronger oxidizing agents (Cu, Ag salts) splitting of the bonds of these enols takes place. Thus a great variety of substances is produced (carbon dioxide, formic acid, glycolic acid, oxalic acid, etc.) having from one to five carbon atoms.

The extent of degradation is a function of temperature, of alkali concentration, and of time. Thus in the quantitative oxidation of a monosaccharide the conditions must be worked out empirically. The extent of reduction of Fehling's solution by glucose, for example, is much greater than could be accounted for by the simple oxidation of one aldehyde group to carboxyl; this is of course due to the fact that more than one carbon atom is oxidized. In the study of the equilibrium mixture formed in the alkaline oxidation of glucose, scores of different derivatives have been found. This ready dissociation (fragmentation) of glucose suggests its extreme importance in the biochemical processes of the living organism.

(3) *Reduction*. Sodium amalgam in water reduces monosaccharides to the corresponding alcohols (glucose to sorbitol). Vigorous reduction gives saturated hydrocarbons.

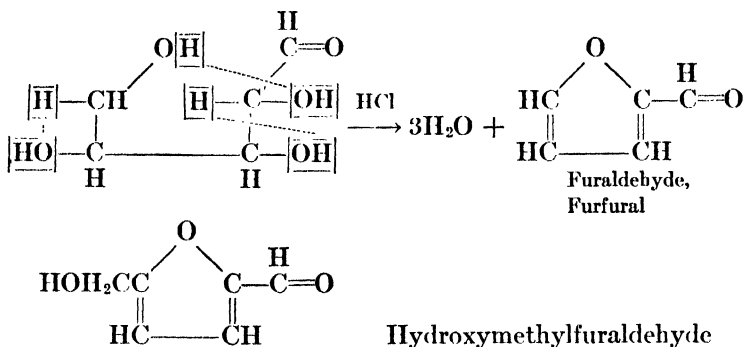
(4) *Reactions of hydroxyl group*. Monosaccharides form esters, ethers, and salts as would be expected from compounds having OH groups. The

\* Gluconic acid may be made in good yield by action of *Aspergillus niger* on glucose. This is of interest since gluconic acid has commercial value. About 500,000 pounds a year is used in medicine, in tanning, and otherwise.



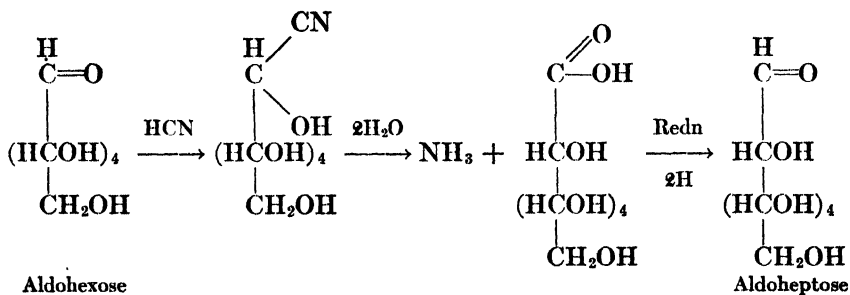
ethers will receive further mention. Monosaccharides are very feeble acids ( $K_a$  for glucose is  $6.6 \times 10^{-13}$ ), however they are more acidic than simple alcohols. Thus glucose can dissolve calcium oxide to form a glucosate, soluble in water.

(5) *Pentoses by dehydration produce furfural*, while hexoses give hydroxymethylfurfural. The method of formation of furfural from a pentose is shown in the following scheme:

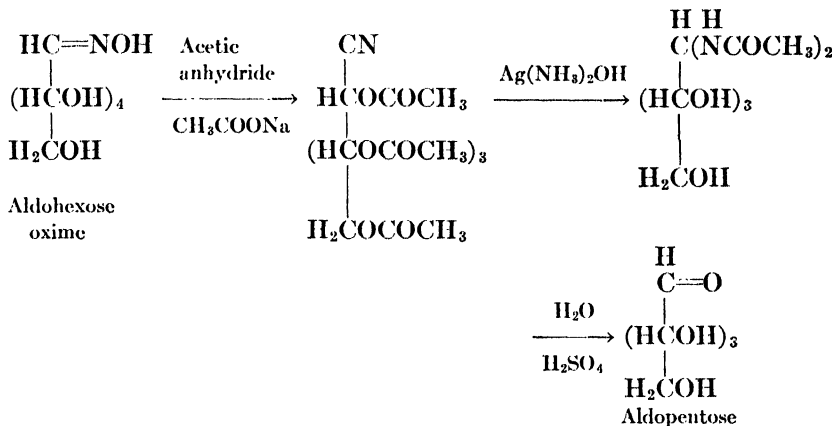


The production of furfural from carbohydrates by the dehydrating action of concentrated sulfuric acid is presumed to be the basis of the Molisch reaction which is used as a general test for carbohydrates. In this test the carbohydrate solution, to which some  $\alpha$ -naphthol has been added, is layered over concentrated sulfuric acid. A colored ring appears at the junction of the liquid layers. For uses of furfural, see page 641.

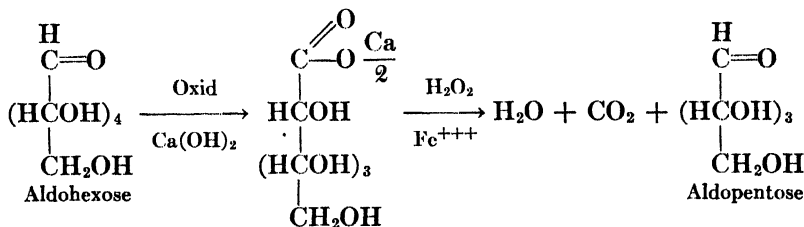
(6) *Adding carbon to an aldose* ("stepping up"). Kiliani reaction. The aldose is first brought into reaction with hydrogen cyanide, forming thereby its cyanohydrin. The latter upon hydrolysis is converted into a polyhydroxy acid having one more carbon than the original aldehyde sugar. Reduction of the lactone of the acid to aldehyde completes the synthesis. The equations for the reactions are shown in semi-diagrammatic form below:



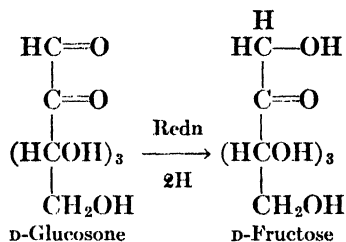
(7) *Taking carbon from an aldose. Wohl method.* The oxime is made from the aldose by the use of hydroxylamine. Treatment with acetic anhydride acetylates the sugar and changes the oxime to the nitrile. Treatment with ammoniacal silver oxide removes the acetyl groups, forming the diacetamide derivative of the aldose with one less carbon. This upon acid hydrolysis gives the free aldose.



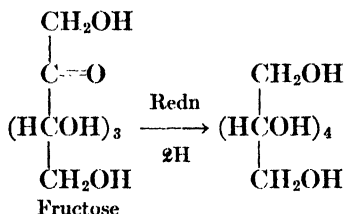
*Ruff method.* The aldose is first oxidized to the corresponding acid, whose calcium salt is treated with hydrogen peroxide in the presence of a ferric salt. Carbon dioxide is lost; at the same time the carbon next the carboxyl group is oxidized. The result of these reactions is the production of an aldose having one less carbon atom than the initial compound. The following scheme shows the successive steps:



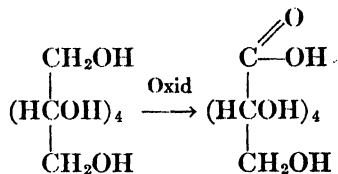
(8) *Transformation of an aldose to its isomeric ketose.* This is illustrated by the change of glucose to fructose. This conversion and its reverse are effected by reactions brought to bear upon the osone, which it will be remembered is formed by the hydrolysis of the osazone (note equation on page 350). If the osone be reduced by use of zinc and acetic acid, its aldehyde group will be reduced to alcohol; fructose is formed in this way from glucose:



(9) *Transformation of a ketose to its isomeric aldose.* As an example we take the change of fructose to glucose. For this conversion the ketose is first reduced to a hexahydroxy alcohol:

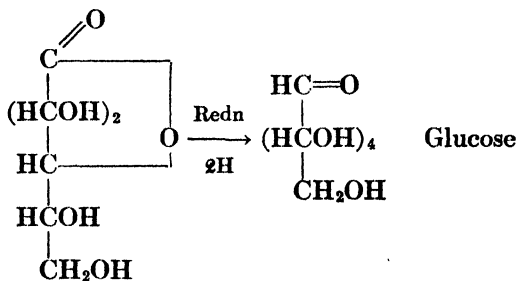


Oxidation of this alcohol yields a monocarboxylic acid:



Reduction of the lactone of the acid gives glucose.

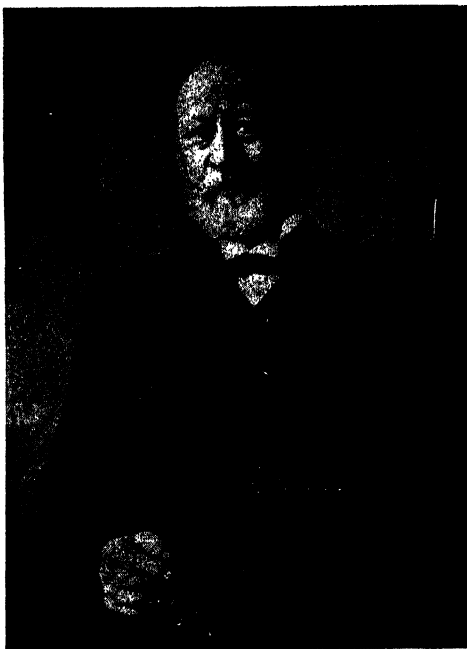
The *gamma* lactone, most stable of those possible, is the one usually obtained from an aldonic acid.\* Lactones of this type form very readily. Unlike the acids they may easily be reduced.



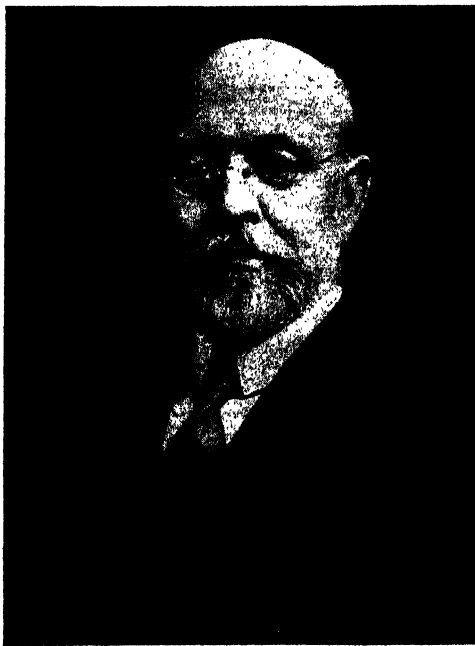
Other pairs of sugars, related to each other as are glucose and fructose, may similarly be changed one to the other. Comparison of the graphic

\* Aldonic acids have the formula  $\text{HOCH}_2(\text{CHOH})_x\text{COOH}$ .

CARL T. LIEBERMANN. (1842-1914, German.) Liebermann did a great deal of work in connection with dyes. His joint synthesis of alizarin with Graebe is well known. He also worked with cochineal. In addition he carried on work with anthracene and anthraquinone compounds, and with cocaine. See *J. Chem. Education*, **7**, 2609 (1930), *J. Soc. Chem. Ind.*, **34**, 128 (1915); also this book, page 692.

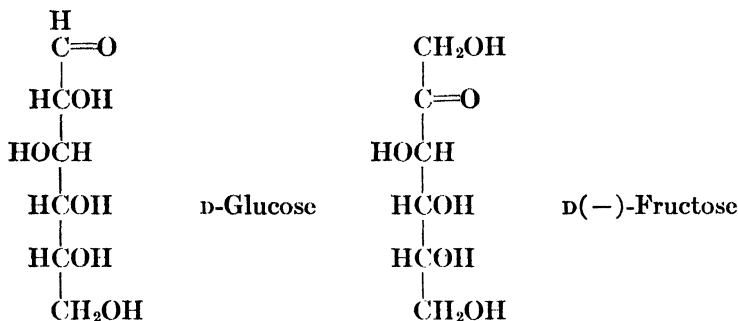


*Berichte*, **51**, 1135 (1918).

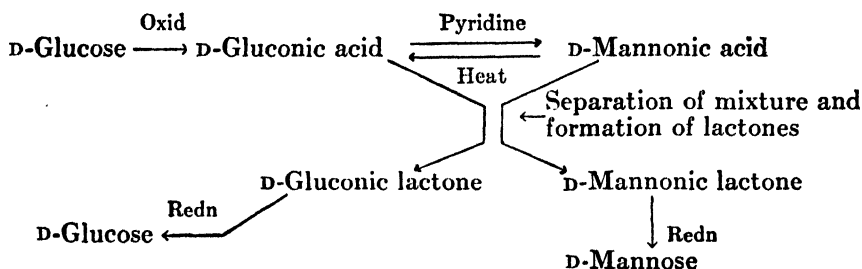


IRA REMSEN. (1846-1927, American.) Discoverer (with Fahlberg) of saccharin. Prominent research worker, teacher, and writer. Author of a popular organic text and other chemistry books. He founded the *American Chemical Journal*. Remsen was professor of chemistry, later president, of Johns Hopkins University (1901-1912). See *J. Chem. Soc. (London)*, **129**, 3182 (1927). Harrow, pp. 197, 428, *J. Chem. Education*, **6**, 1282 (1929), **16**, 353 (1939); *J. Am. Chem. Soc.*, **50**, 67 (1928).

formulas of glucose and fructose shows plainly that conversion of one to the other involves changes on the first two carbons only.



(10) *Transformation of an aldose to its epimer.* It will be remembered that epimeric compounds have identical structures except for carbon atom #2. The H and OH at this point can be made to reverse their positions by heating the aldonic acid with pyridine. Thus, glucose and mannose are epimers. For the transformation of the former to the latter it is first oxidized to gluconic acid, then treated with pyridine. As the shift of H and OH at the *alpha* position is reversible, a mixture of gluconic and mannonic acids results. These are separated by customary chemical procedure; they are not optical isomers, hence differ in physical properties. Reduction of the lactone of mannonic acid yields mannose. The scheme below outlines the steps.

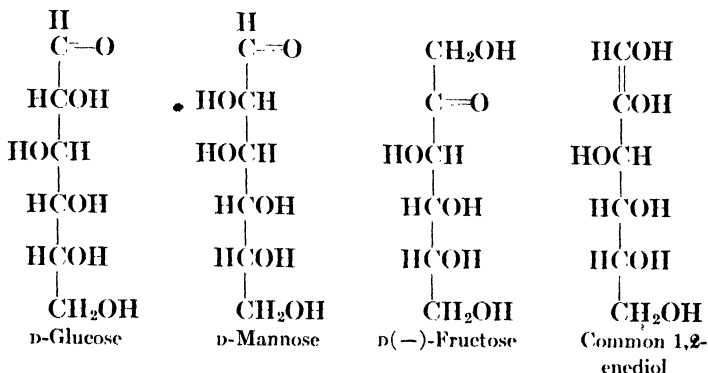


This process is known as **epimerization**.

**Asymmetric Synthesis.** In carrying out the reaction shown on page 354, in which a new asymmetric carbon atom is added to an aldose, two epimers are formed, but since the original substance is optically active, the epimers are not formed in equal amounts (asymmetric synthesis). Thus in going from xylose to the epimers gulose and idose (see chart, page 346) we secure more of the former than of the latter, and mannose by HCN synthesis gives only D-mannoheptonic acid.

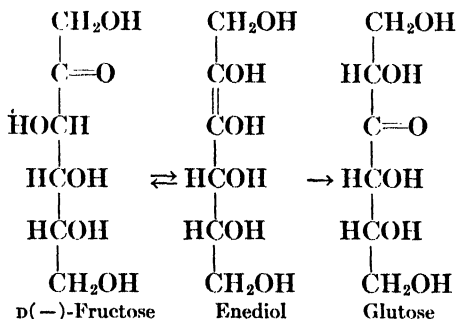
(11) *Lobry de Bruyn transformation.* When glucose is treated with extremely dilute alkali the molecule rearranges. An equilibrium mixture

of D-glucose (63.4%), D-mannose (2.4%), D(-)-fructose (30.9%), and D-glucose results. The same mixture is obtained if we begin with D(-)-fructose or D-mannose. It is believed that the changes are possible because (1) any one of these sugars gives its 1,2-enediol with alkali treatment, and (2) because each gives the same 1,2-enediol.



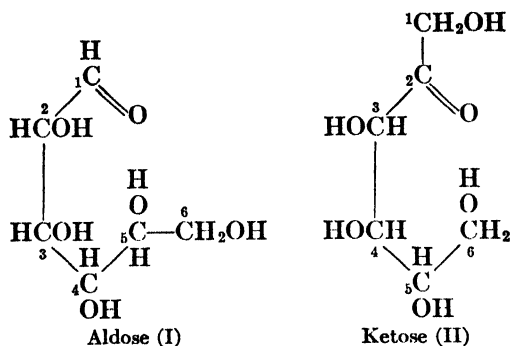
Inspection of the formulas shows that these three sugars differ only with regard to carbons 1 and 2, and the difference disappears in the common enol form. Thus the enol can rearrange to form any one of the three. This interesting transformation is highly significant in view of the fact that these hexoses are so important among the natural sugars.

The formation of glucose is laid to a 2-3 enolization of fructose:

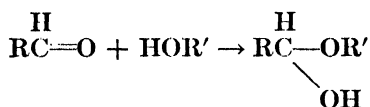


### MONOSACCHARIDE RING STRUCTURES

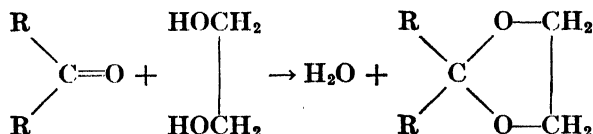
Up to this point the formulas for monosaccharides have been shown as straight chains. This was done because with this type of structure the relationship between various sugars is easily seen, also because it is the conventional way to show aliphatic compounds. We realize that because of the angles between bonds of the carbon atoms of a chain it can form a ring (see pages 39, 611). Thus the ends of a six-carbon chain approach each other as shown below, and there is opportunity for reaction between the carbonyl group and the OH groups on the terminal carbon atoms:



Aldehydes react with alcohols by addition to form hemiacetals:



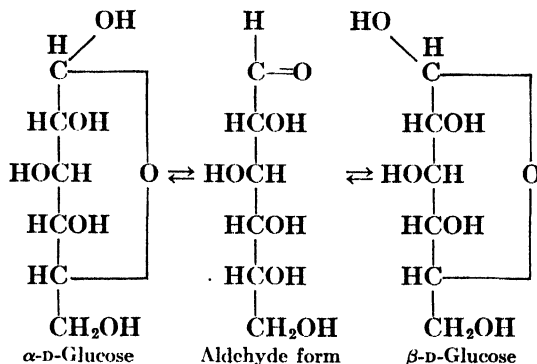
Ketones also undergo a similar reaction when stable ring formation is possible:



Such a reaction in the case of a monosaccharide would give a ring structure. It is not likely that in (I) the OH of carbon 6 would be involved, because a 7-atom ring would result, and experience has shown that 6- and 5-atom rings are more easily formed. Rings of four atoms or less do not form easily, so that carbon atoms beyond 4 are not so much concerned.

There is much evidence that such ring forms actually exist. For example glyceric aldehyde, which could not easily form such a ring, shows all common aldehyde properties, while tetroses and higher aldoses do not. The reducing and aldehyde properties of glucose do not show themselves promptly in the cold and are rather slow even upon the application of heat. A still more decisive proof is furnished by the phenomenon of mutarotation and the existence of isomeric glucosides.

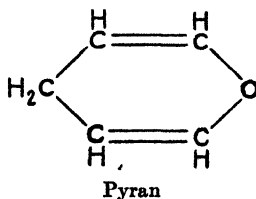
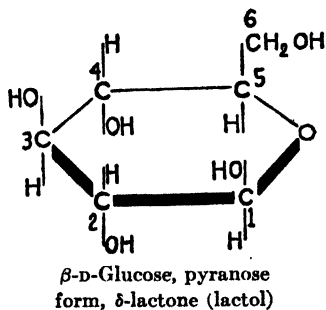
**Mutarotation.** Two forms of glucose are known, one having an optical rotation of  $+113.4^\circ$  the other of  $+19.0^\circ$ . As has been said, glucose is reluctant to show true aldehyde properties. Both of these phenomena are explained if we assume that glucose has a ring structure as shown in the following formulas. In this form it is not an aldehyde, and before it can act as such, the ring must be broken. The two different structures possible when this ring is included in the molecule account for the two different forms of glucose which have been observed.



All three forms,  $\alpha$ -ring form,  $\beta$ -ring form, and aldehyde form exist in equilibrium with each other in solution.\* In fact if a solution be made of either the  $\alpha$ -form having  $[\alpha]_D = +113.4^\circ$  or the  $\beta$ -form of  $[\alpha]_D = +19^\circ$ , the rotation value will change until it becomes  $+52.2^\circ$ , which is evidently the rotation of an equilibrium mixture (37%  $\alpha$ , 63%  $\beta$ ). This phenomenon of change in rotation is known as *mutarotation*. The aldehyde carbon becomes asymmetric when the molecule of glucose assumes the ring form. Thus additional "lactone" form isomers of glucose must be added to the number made possible by the four asymmetric carbon atoms normally present in the molecule. The phenomenon of mutarotation is not peculiar to glucose but is shown by most of the simple sugars. The forms shown above ( $\delta$ -“lactone” forms) appear to be the structure in which most of a sample of glucose exists. The  $\gamma$ -“lactone” form represents a labile and very reactive molecule. *Gamma* glucose has not been isolated but derivatives of it have been made.

The ring form having a 5-atom ring (*gamma* “lactone”) is known as the furanose form since the ring resembles that of the compound furan; the 6-atom ring form is known as the pyranose form because of the resemblance to pyran.† The formulas given here are somewhat easier to visualize

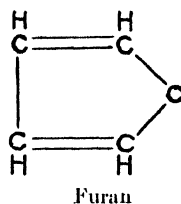
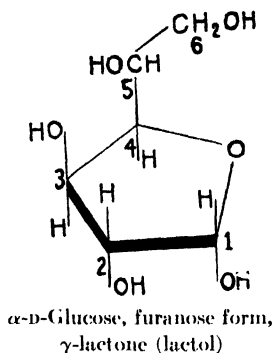
*Ring Formulas for Glucose.*



\* About 0.03 per cent is in the free aldehyde form.

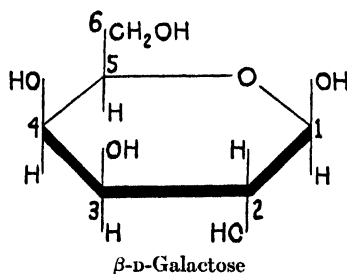
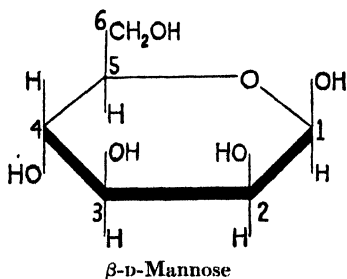
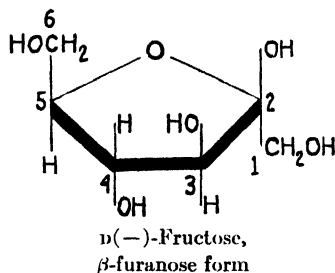
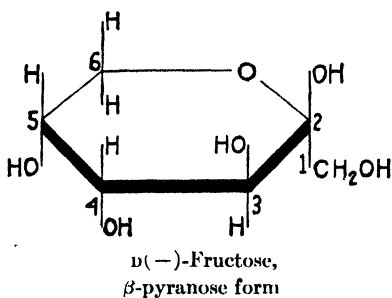
† This formulation was proposed by Haworth. For an illuminating discussion see his papers in *J. Soc. Chem. Ind.*, **46**, 295 (1927) and **54**, 859 (1935).





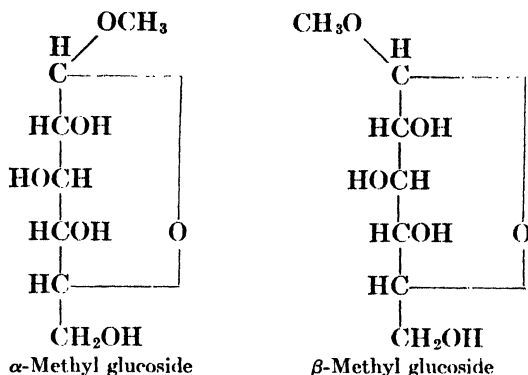
than those with the carbons in a straight line. In order to avoid confusion with true lactones these ring forms are known as *lactols*. They are diagrams of molecular models. The heavy lines indicate that part of each model which is nearest the observer. The drawings should be compared with actual models made from "Tinker-Toy" assortments of atomic models.

*Ring Formulas (Fructose, Mannose, Galactose).*



**Glucosides.** When Emil Fischer treated glucose with methyl alcohol saturated with dry hydrogen chloride, he obtained the methyl glucosides.

These are pictured below.



These compounds do not show aldehyde properties nor do they display mutarotation. These facts can only be explained on the basis of a ring structure, and they also show that the ring is fixed and that it involves the aldehyde carbon atom. The forms shown here are the pyranose forms.

**Additional Data.**  $\alpha$ -Methyl glucoside is dextrorotatory; split by maltase (maltase splits  $\alpha$ -glucosides). Synthesis from anhydrous glucose and methyl alcohol with hydrogen chloride.  $\beta$ -Methyl glucoside, levorotatory; split by emulsin (emulsin splits  $\beta$ -glucosides). Synthesis from *hydrated* glucose, alkali, and dimethyl sulfate. Treatment of a mixture of  $\alpha$  and  $\beta$  glucosides with yeast gives the pure  $\beta$  compound. The  $\alpha$  form is split by the maltase of yeast and the glucose is then fermented by the zymase of the yeast.

**Proof of Structure of the Glucosides. Methylation.** Only one OH group (the "aldehydic" OH) of glucose will react with alcoholic hydrogen chloride. Evidently this is more reactive than the other four ("alcoholic") OH groups.\* The methylation of the other hydroxyls can be accomplished by the use of dimethyl sulfate and alkali. The hydrolysis of the methylated glucoside affects only the "glucosidic" ether, which again proves the enhanced reactivity at this point. The other four ether groups remain intact. Oxidation then splits the molecule where the oxygen bridge joins the chain, and examination of the resulting compounds shows at what carbon the bridge was attached.

Compounds of the same type as  $\alpha$  and  $\beta$  methyl glucosides, formed by the reaction of glucose and hydroxylic substances, are known as glucosides. They are rather frequently found in nature. The general term is glycosides. Several of these are listed in Chapter XXXVIII. A physiological interest attaches to the glycosides because when certain deleterious substances (car-

\* D-Glucose, D-mannose, D-galactose, and a number of glucosides treated with heavy water suffered an exchange of hydrogen for deuterium which seemed to involve only the active hydrogen of the hydroxyl groups.

bolic acid, camphor, aniline, chloral) are taken into the body, they are made less harmful by being combined with glucose. The resulting glucosides are then eliminated in the urine after a preliminary oxidation to glucuronic acid derivatives.

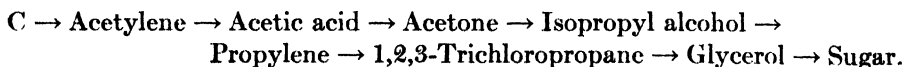
### SYNTHESIS OF MONOSACCHARIDES

The method presented on page 354 for adding carbon to an aldose may be used to build up a monosaccharide from the homolog having one less carbon. By repetition of the procedure successive carbon atoms may be added. By using this synthesis Fischer prepared aldononoses from aldohexoses. In addition to this method we have the oxidation of a polyhydroxy alcohol to its aldehyde:



**Syntheses from Formaldehyde, Glycerol.** If a solution of formaldehyde, saturated with calcium hydroxide, is allowed to stand for some time it will be found to contain a mixture of sugars (formose) one of which is a form of fructose. Mild oxidation of glycerol gives glycerose, a mixture of glyceraldehyde and dihydroxyacetone. These were condensed by E. Fischer to a mixture of  $\alpha$  and  $\beta$  acrose, a ketohexose whose osazone was inactive but otherwise like that of glucose. *Alpha* and *beta*-acrose were also made from the three carbon compound, acrolein dibromide, by treatment with barium hydroxide.

By methods which cannot be given here Fischer showed that  $\alpha$ -acrose was *dl*-fructose. He made from this the following: *D*-glucose, *L*-glucose, *D*(-)-fructose, *L*(+)-fructose, *D*-mannose, *L*-mannose. *Beta* acrose was later shown to be *dl*-sorbose, a ketohexose analogous to fructose. Since glycerol may be made from acetic acid, and this in turn from acetylene, we have here a laboratory synthesis of natural sugars from coal, surely a remarkable triumph for the organic chemist.



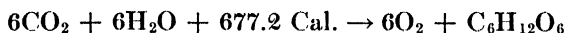
The fact that sugar has been made in the laboratory from formaldehyde has led to the formulation of the theory that in plants the formation of starches and sugars is preceded by production of formaldehyde.

### PHOTOSYNTHESIS

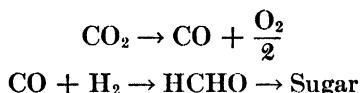
By all odds the most important chemical reaction mechanism in nature is that by means of which the carbohydrates are synthesized. Through these reactions the plants lay up stores of sugars, starches, and cellulose and from the simple sugars synthesize the proteins and fats and other complex substances. The reactions are fundamental to man's existence since we obtain our main food supplies thereby. They are fundamental too for the

industrial chemical developments of our time. We recognize that not only our present food supply depends upon photosynthesis, but that to it we owe the stores of coal and petroleum accumulated in past ages.

Despite the vast amount of work devoted to study of photosynthesis the mechanism is but imperfectly understood. It is known that plants take in carbon dioxide and utilize water and that they give off oxygen. The presence of chlorophyll, the green coloring matter of the plants, is essential and the radiant energy of the sun is the driving force. The chemistry may be summarized in the following overall equation:



Baeyer originally proposed that the reduction of carbon dioxide produced formaldehyde, and that the simple sugars were then formed by condensation of the formaldehyde.



Subsequently several investigators claimed to have found formaldehyde in green leaves. The fact that certain plants can form starch when immersed in weak formaldehyde or acetaldehyde solutions is important in this connection.

Another form of attack of the problem consists in the illumination of solutions of carbonic acid with light of various wave lengths. Carbohydrates have apparently been made in this way. It is claimed that formaldehyde can be made by illumination of carbonic acid, also claimed that illumination of formaldehyde solutions has produced simple sugars. It has not been possible, however, to carry on these syntheses on a useful scale so as to compete with the plants (also many investigators report negative results). Nor can it be said that the reaction mechanism given here has been positively confirmed. In fact, recent work using carbon dioxide containing radioactive carbon does not uphold the theory that formaldehyde is a precursor to sugar formation. The radioactive carbon was recovered as a constituent of carboxyl group in molecules having a molecular weight of about 1000.

When glucose is oxidized in the body the energy originally stored in the compound is released (about four Calories per gram oxidized). Fats have a far higher energy content than carbohydrates (about 9 Cal. per gram). Thus the oxidation of the foodstuffs is our means of getting life energy from the sun. The plant itself receives and uses but a small part of the available energy from the sunlight for the making of carbohydrates, since only part of the light is intercepted in the first place, and of that a portion is reflected from the leaves. If we consider only that part of the light actually absorbed by the leaf and finally represented by available carbohydrate, the efficiency of the process seems low. But when one takes into consideration the fact

that much of the incoming energy was used for the life processes of the plant during the growing season, the efficiency proves to be good.

Whether glucose is the first sugar formed in the plant has not been determined with certainty. It is known that plants can utilize glucose solution and lay up starch. Also it has recently been shown that sugar cane leaves kept in the dark and supplied with either glucose or fructose or a mixture of these, can form cane sugar. Further research may soon supply the missing links in the chain of photosynthesis. There is little doubt that glucose plays a very important part in the process.

### HUDSON'S RULES

An inspection of the formulas for  $\alpha$ - and  $\beta$ -methyl glucosides on page 363 will show that the only essential difference between them lies in the space disposition of the  $\text{OCH}_3$  group. They are otherwise identical. Likewise in  $\alpha$ - and  $\beta$ -glucose, page 361, the only difference has to do with the "glucosidic" OH group. Call the rotation due to the end asymmetric carbon (A) and that due to the other four asymmetric carbons (B). Then for one "lactone" isomer the molecular rotation will be (A) + (B) and for the other  $-(A) + (B)$ . Their sum is  $2(B)$ , their difference  $2(A)$ .

Example:

	Sum	Difference
$\alpha$ -D-Glucose		
Molecular rotation $(180 \times 113) = 20,340$		
$\beta$ -D-Glucose		
Molecular rotation $(180 \times 19) = 3,420$ .....	23,760	16,920

From the above we get, (B) = 11,880. Now consider the  $\alpha$ - and  $\beta$ -methyl glucosides. (B) will again be the molecular rotation due to the four asymmetric carbons within the molecule (arrangement identical with that of glucose). The end carbon atom now holds  $\text{OCH}_3$  instead of OH, therefore the rotational effect will be different from the former value; call it ( $\hat{A}$ ). The molecular rotation of one isomer will be ( $\hat{A}$ ) + (B) and that of the other  $-(\hat{A}) + (B)$ . The sum is  $2(B)$  and if there is any validity to the reasoning employed here, the same result should be had as in the previous example.

Proof:

	Sum
$\alpha$ -Methyl-D-glucoside	
Molecular rotation $(157 \times 194) = 30,460$	
$\beta$ -Methyl-D-glucoside	
Molecular rotation $(-32 \times 194) = -6,200$ .....	24,250

The value of (B) calculated from this is 12,125 which agrees well with the 11,880 calculated from glucose. Other interesting and practical relationships (Hudson's rules) reached by methods similar to the above are shown in the original papers, which should be consulted.

### ISOMERISM OF MONOSACCHARIDES

As stated on page 339 the number of optical isomers for an active compound is given by the expression  $2^n$ , where n states the number of asymmetric carbon atoms in the molecule. Thus an aldotriose will have two such isomers, an aldotetrose will have four, an aldopentose eight,

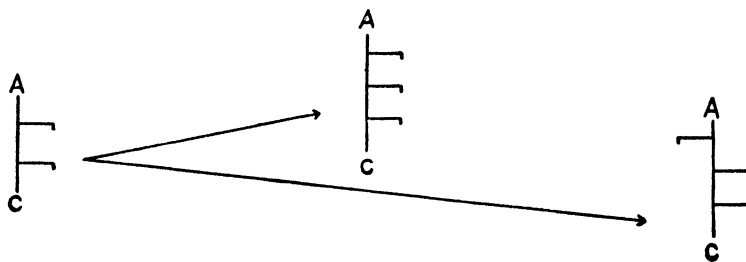
and so on, the number of optical isomers being doubled for every additional asymmetric carbon atom in the compound. The two aldotriose molecules, D and L, will be mirror images of each other. Similarly the aldotetroses, aldopentoses, etc., will exist in pairs, each D-compound having a corresponding L-compound which is its mirror image. Thus for the aldotetroses and higher aldoses and ketoses we have a D-family and an L-family of compounds.

### CONFIGURATION OF MONOSACCHARIDES

It is a relatively simple affair to sketch on paper all the possible space arrangements for H and OH in the eight aldopentoses or the sixteen aldohexoses, but to take a given sugar and tag it with its proper label is quite another matter. Much of the pioneer work in this field was accomplished by Emil Fischer. It is rightly considered as an outstanding achievement in the organic chemical field. It is not proposed to review all of this work here, but rather to indicate the type of reasoning which is involved by working out the structures of the aldopentoses. We will concern ourselves only with the D-family, as the reasoning would be just the same for the L-family. As a preliminary step the several reactions and concepts to be used in the argument will be reviewed.

(1) It has been shown that glucose by oxidation yields first a monocarboxylic acid (oxidation of aldehyde group), and next a dicarboxylic acid (oxidation of terminal primary alcohol group). The aldopentoses by a similar sequence of oxidation yield, finally, trihydroxyglutaric acids,  $\text{COOH}(\text{CHOH})_3\text{COOH}$ .

(2) The method of lengthening the carbon chain of an aldose sugar is given on page 354. When these reactions are carried out on a given aldose two new aldoses are produced, having H and OH on carbon #2 in opposite placements.\*



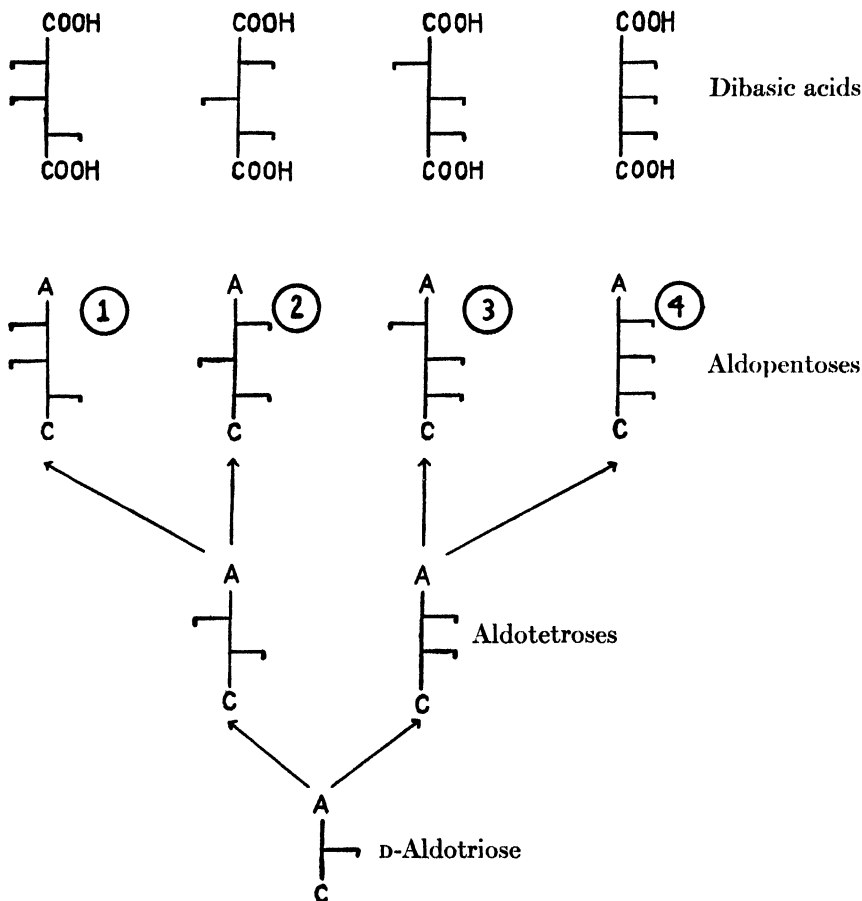
(3) When an aldose forms an osazone, only the terminal aldehyde group and the secondary alcohol group in the next position are affected. If, therefore, two monoses give an identical osazone, the space disposition of H and OH for all carbon atoms beyond the first two carbons must be the same in each compound. This was brought out previously with reference to glucose and fructose.

Let us begin with the aldotrioses. There are two of these; we will confine our attention to the D-compound only, and by convention we show this with the OH group to the right-hand side. When this is treated with HCN, etc., two aldotetroses will result as shown in the diagram on the next page. If each of these compounds is given the HCN treatment, the four D-aldopentoses will result.

Above the aldopentoses are shown the dicarboxylic acids formed by their oxidation. It will be noted that the acids from 1 and 3 are optically active, while those from 2 and 4 are inactive by internal compensation (see page 338). Note also that 1 and 2 will give an identical osazone, as will 3 and 4.

\* In the symbols used here, A stands for the aldehyde group, and C for the terminal primary alcohol group. The side lines carrying vertical strokes at the end show OH groups; an H atom is to be imagined opposite each of these.

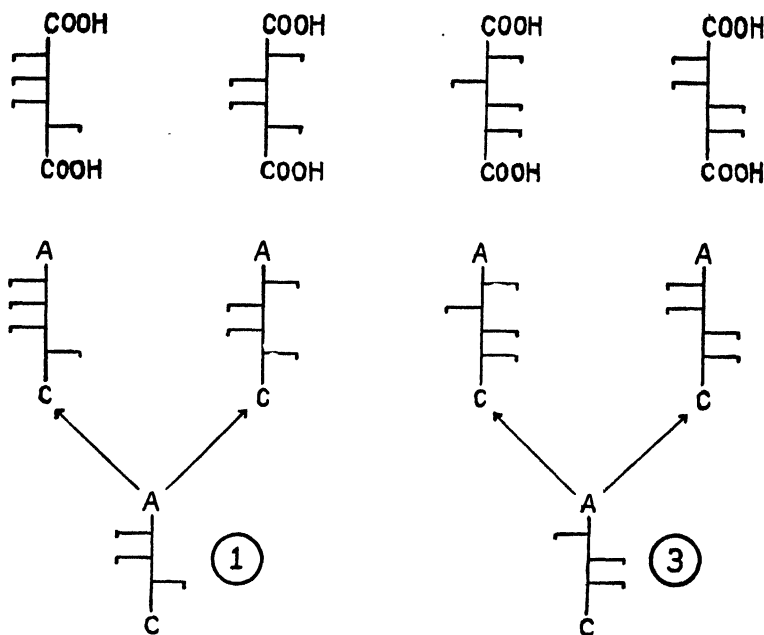
We may now proceed to examine the actual aldopentoses. They are called arabinose, ribose, lyxose, and xylose. Arabinose and ribose give an identical osazone. Hence they are pair 1 and 2 or 3 and 4. The oxidation of arabinose and of lyxose gives acids which are optically active; this corresponds to pair 1 and 3. Xylose and ribose give upon oxidation dicarboxylic acids which are inactive and not resolvable, hence inactive by internal compen-



sation; this tallies with pair 2 and 4. Likewise, the acids obtained from xylose and ribose are not identical, and this agrees also with our diagram..

We have thus shown that xylose and ribose are 2 and 4, and that lyxose and arabinose are 1 and 3. In neither case could we say which formula of a pair to assign to which sugar. The question can be settled as follows: treat 1 and 3 with HCN, etc., to add one carbon to the chain, hydrolyze the resulting cyanohydrins, then oxidize the monocarboxylic acids obtained to the dicarboxylic six-carbon acids. Formulas of these compounds appear on p. 369.

It is readily seen that 1 gives an active and an inactive acid, while 3 gives two acids, both active. In actual practice arabinose yields two active acids by the treatment outlined, while lyxose gives one active and one inactive acid. Thus arabinose has the configuration shown in 3, and 1 stands for lyxose.



It has been said that arabinose and ribose give an identical osazone. Thus if arabinose is shown by formula 3, ribose must be 4. By elimination 2 is xylose. The configuration of the aldohexoses is worked out in much the same manner as has been indicated for the aldopentoses. The configurations of the ketoses of a given number of carbon atoms follow from those of the aldoses of like carbon content, by noting which ketoses and aldoses give identical osazones.

The *delta* lactol and *gamma* lactol forms of glucose are shown on pages 361, 362. Glucose can also exist in other ring forms, and beyond doubt all of the monoses show this form of isomerism, each having several ring structures which, in a solution, exist in equilibrium with the open-chain compounds. In such an equilibrium mixture the most stable molecular forms would predominate.

The proof of structure which has just been given rests upon reactions of the aldehyde (open-chain) forms of the sugars, and the fact that ring forms also exist has no bearing on the matter. The reactions used in this work pertain to the aldehyde form of the sugar, and as this is used up by the reagents, the ring forms which are in the equilibrium mixture will revert to the aldehyde form, according to the laws which govern such equilibria.

## DISACCHARIDES

We have noted the ability of the "aldehydic" hydroxyl of monosaccharides to form ethers with simple alcohols and other hydroxylic compounds. The synthetic and natural glycosides result from this reaction. Similarly this active hydroxyl of a monosaccharide may react with hydroxyl group of a second molecule of monosaccharide. Disaccharides and polyoses are formed in this way. The union may be between a hexose and a pentose, a pentose and a pentose, etc. Since the hexoses are so plentiful in nature, we



should expect to find the hexose-hexose type in abundance. This is the type which chiefly interests us and the only type to be considered here.

TABLE 30.—CONSTANTS OF SOME MONOSACCHARIDES

Name	M.p.	$[\alpha]_D$	Epimer	Osazone, M.p.
D-Erythrose.....	.....	— 14.5*	Threose	164
L-Erythrose.....	.....	+ 21.5†	.....	163-4
$\alpha$ -D-Arabinose.....	159.5	— 54.0	Ribose	160
$\beta$ -D-Arabinose.....	159.5	—175.0	.....	.....
Eq. Arabinose.....	159.5	—105.0	.....	.....
$\alpha$ -L-Arabinose.....	159.5	.....	.....	.....
$\beta$ -L-Arabinose.....	159.5	+186.0	.....	160
Eq. Arabinose.....	159.5	+105.9	.....	.....
$\alpha$ -D-Xylose.....	145	+ 92.0	.....	159
$\beta$ -D-Xylose.....	.....	— 20.0	.....	164
Eq. Xylose.....	.....	+ 19.0	.....	.....
$\alpha$ -L-Xylose.....	153	+ 9.2†	.....	.....
Eq. L-Xylose.....	153	+ 18.5†	Lyxose	163
$\alpha$ -D-Lyxose.....	106-7	+ 5.5	.....	164
$\beta$ -D-Lyxose.....	117-8	— 70	.....	164
Eq. Lyxose.....	105	— 14	Xylose	.....
$\alpha$ -D-Ribose.....	95	.....	.....	166
Eq. Ribose.....	87	.....	Arabinose	.....
Eq. L-Ribose.....	.....	+ 18.8	.....	.....
$\alpha$ -D-Mannose.....	132	+ 34.0	Glucose	.....
$\beta$ -D-Mannose.....	132	— 17.0	.....	.....
Eq. Mannose.....	132	+ 14.0	.....	208 dec.
Eq. L-Mannose.....	132	— 14	.....	205 dec.
$\alpha$ -D-Glucose.....	146	+113.4	Mannose	208 dec.
$\beta$ -D-Glucose.....	150	19.0	.....	.....
Eq. Glucose.....	.....	52.2	.....	.....
$\alpha$ -L-Glucose.....	146	—113.4	.....	.....
$\beta$ -L-Glucose.....	.....	— 19.7	.....	.....
Eq. Glucose.....	150	— 51.4	.....	205 dec.
$\alpha$ -D-Galactose.....	168	+144.0	Talose	186
$\beta$ -D-Galactose.....	168	+ 52	.....	186
Eq. Galactose.....	168	+ 80.05	.....	196
$\alpha$ -D-Gulose.....	.....	+ 61.6	Idose	168
$\beta$ -L-Gulose.....	.....	— 20.4	.....	156
$\alpha$ -D-Fructose.....	.....	+ 34	.....	208 dec.
$\beta$ -D-Fructose.....	105	—133.5	.....	.....
Eq. Fructose.....	.....	— 93	.....	.....

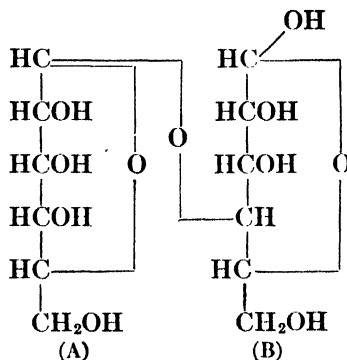
\* Equilibrium value.

†  $\lambda = 7580 \text{ \AA}$ .

**Reducing and Non-reducing Disaccharides.** When the aldohexose (A) unites with hexose (B) it loses its aldehyde properties and in addition the lactol ring is "locked." If molecule (B) reacts with (A) by means of its aldehydic hydroxyl then it too loses aldehyde properties; the resulting disaccharide is non-reducing. The lactol ring of (B) also is "locked."

If (B) unites with (A) by using some OH group other than the aldehydic group, the latter is free to display its usual reactions. Residue (B) then shows reducing properties, can undergo mutarotation, and form an osazone. It can likewise form a glycoside with a third molecule. The formulas below bring this out.

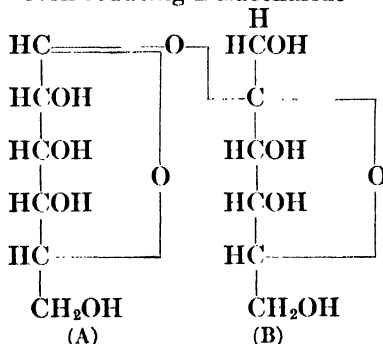
### Reducing Disaccharide



Aldehyde properties absent; Lactol ring "locked."

Has potential aldehyde properties; Lactol ring not "locked." Can show mutarotation; hence the disaccharide can exist in  $\alpha$  and  $\beta$  forms.

### Non-reducing Disaccharide



Aldehyde properties absent; Lactol ring "locked."

Aldehyde properties absent; Lactol ring "locked."

The disaccharides of greatest interest are sucrose, maltose, lactose, and cellobiose. Sucrose is non-reducing, the other three are reducing sugars. The fundamental difference in structure between the two types as brought out above has the consequences shown in the table on page 372.

These disaccharides are crystalline solids whose solubilities are like those of simple sugars. As shown in the table (over) the reducing disaccharides have chemical reactions like those of glucose.

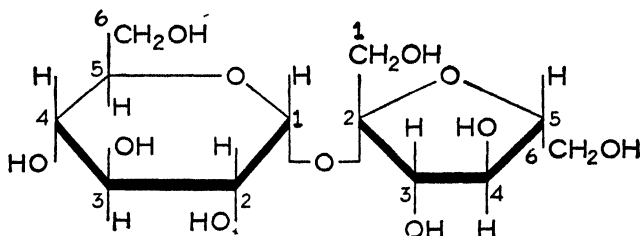
**Sucrose.** Sucrose, or cane sugar, is a constituent of the sap of many trees, notably the sugar maple. Ripe fruits are rich in this sugar. It is

	Forms glycosides	Splitting by alkali (page 356)	Fehling test	Osazone formation	Muta-rotation
Sucrose.....	—	—	—	—	—
Maltose.....	+	+	+	+	+
Lactose.....	+	+	+	+	+
Cellobiose.....	+	+	+	+	+

commonly obtained from cane juice or from sugar beets, by a process which provides for the precipitation of impurities and colored substances, and the partial evaporation of the juice until crystallization sets in. The annual world production of sucrose is about 30,000,000 tons, of which about two-thirds is from cane and one-third from beets. Principal use is for food, but very determined research is in progress to find commercial uses.

Sucrose is dextrorotatory, but upon hydrolysis it yields equal quantities of glucose and fructose, the sum of whose rotations is negative. Hence this hydrolysis mixture is called *invert sugar*, and hydrolysis of sugar is termed *inversion*. Inversion can be carried out by the use of acids or alkalies; it is likewise catalyzed by an enzyme, invertase, found in certain yeasts.\* Although sucrose is not directly fermentable, its hydrolysis products are, and in cases where invertase and zymase both are present, hydrolysis and fermentation succeed each other, effecting a conversion of the sucrose to carbon dioxide and alcohol.

Sucrose does not respond to tests for the carbonyl group,† and it is for this reason assumed that the “aldehydic” groups of both glucose and fructose are involved when sucrose is formed by the union of these two. The following is a proposed structure of sucrose (Haworth).



Sucrose  
 $\alpha$ -D-Glucopyranosyl  
 $\beta$ -D-fructofuranoside

\* The progress of inversion can be followed by noting the changing optical rotation of the mixture. By the same method the strength of a solution of sugar may be ascertained. Polarimeters, fitted with a special scale so as to read per cent of cane sugar, are known as saccharimeters.

† Sucrose does not reduce Fehling's solution or ammoniacal silver nitrate. It does not react with hydrogen cyanide, and does not form an osazone.

**JOSEPH A. LE BEL.** (1847–1930, French.) Chemistry was an avocation for Le Bel, who was well-to-do. Co-discoverer of the cause of optical activity (van't Hoff). He made the first optically active compound with asymmetric nitrogen atom (1891). See *J. Chem. Soc. (London)*, **1930**, 2789; also this book, page 333.



*Berichte*, **41**, 4505 (1908).

**VICTOR MEYER.** (1848–1897, German.) Meyer did most of his work in the field of organic chemistry (nitroso compounds, oximes, iodonium compounds, thiophene chemistry, steric hindrance), but is also known for work in vapor density determinations. By working at high temperatures the extent of dissociation of various compounds and elements was determined. The Meyer and Jacobson textbook is the best complete text of organic chemistry. See *Am. Chem. J.*, **19**, 812 (1897), *J. Soc. Chem. Ind.*, **16**, 786 (1897), *J. Chem. Soc. (London)*, **77**, 169 (1900), Harrow, pp. 177, 407; also this book, pages 199, 541.

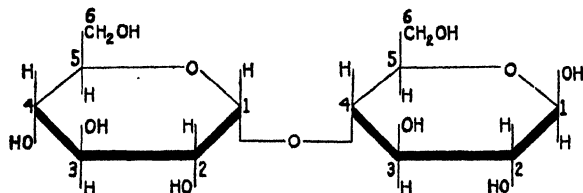
Sucrose is hydrolyzed by organic or by mineral acids, the speed of hydrolysis being proportional to the hydrogen ion concentration. Its acid hydrolysis is about one thousand times as rapid as that of lactose or maltose. This is attributed to the fact that in the formation of sucrose two "aldehydic" (active) OH groups took part.

The alcoholic OH groups of sucrose are able to form salts (example, calcium sucrates) and esters. Like the other disaccharides, sucrose forms an octaacetate. Sucrose octaacetate is used: to make anhydrous adhesives, on paper to make it oil-repellant; as a denaturant in alcohol. Oxidation of sucrose with nitric acid yields oxalic and saccharic acids. When heated to about 200°, sucrose loses water. A brown, syrupy mass called caramel results. This is largely used as a harmless coloring material.

The structures of sucrose and the other disaccharides are learned by methylating the OH groups, hydrolyzing the completely methylated sugar, and identifying the resulting hydrolysis products. The fructose residue of sucrose has the active furanose form, while the glucose residue has the pyranose form. Upon hydrolysis the fructose quickly changes to the more stable pyranose form.

**Maltose.** Maltose is a hydrolysis product of starch, produced from it by the action of an enzyme called diastase, present in barley. The hydrolysis of maltose itself, which yields two molecules of glucose, may be caused by boiling with acid or alkali, or by the use of the enzyme maltase, which is found in yeasts. Maltase splits only  $\alpha$ -glucosides, hence the conclusion that maltose belongs to this group.

Maltose is a reducing sugar. It reacts with Fehling's solution and forms an osazone with phenylhydrazine; that is it contains a potential aldehyde group. The binding of glucose to glucose in its structure involves only one aldehyde group, leaving the other potentially free, as illustrated in the following formula:



Maltose, 4-( $\alpha$ -D-glucosyl)-D-glucose

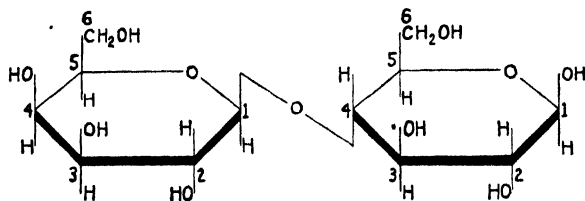
One of the chief uses of maltose is for the preparation of infant foods; it is also used for fountain drinks (Malted milk), and certain prepared foods for adults.

**Lactose.** As might be inferred from its name, the source of lactose is milk. It is obtained from milk by evaporation, after the separation of the fat, and the precipitation of the casein by means of rennet.

Upon hydrolysis the lactose molecule breaks down into a molecule each of glucose and of galactose, an aldohexose whose formula is shown on page

362. Lactose reduces Fehling's solution; hence it is evident that one aldehyde group is not involved in the dihexose union.

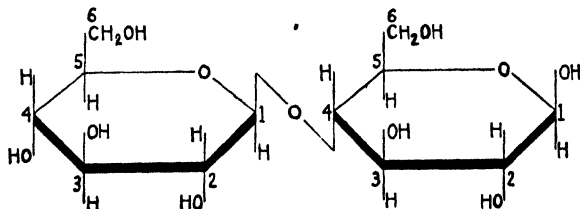
This aldehyde group belongs to the glucose residue, for if we oxidize lactose with bromine-water, and then hydrolyze the resulting compound, we get galactose and gluconic acid, not glucose and galactonic acid.



Lactose, 4-( $\beta$ -D-galactosyl)-D-glucose

Lactose is easily fermented by specific organisms to butyric or lactic acids. The latter is commonly made in this way. Like maltose, lactose is used to make infant foods. It is employed for making candy, for medicines, also as a reducing agent in chemical work. Synthetic lactose was first prepared in 1942 by Hudson.

**Cellobiose.** Cellobiose or cellose can be obtained from cellulose (wood or cotton) by incomplete hydrolysis. Its hydrolysis gives glucose only, as is the case with maltose. However as stated, maltose is split by maltase. For this reason it is taken to be an *alpha* glucoside. Cellobiose on the other hand is split by emulsin, not by maltase. It is judged to be a *beta* glucoside (emulsin splits *beta* glucosides).



Cellobiose, 4-( $\beta$ -D-glucosyl)-D-glucose

### POLYSACCHARIDES OR POLYPOSES

Starch, cellulose, glycogen, and the dextrans, gums, and pectins are included in this group. These are apparently condensation products of the hexoses and other monosaccharides, formed from them by loss of water. Starches, gums, and pectins yield sugars upon hydrolysis and also substances not related to saccharides. In this group we have galactosans, fructosans, etc.; however glucose is the sugar most frequently used. Polyoses are quite insoluble in water or they form colloidal solutions, so that the molecular weights cannot be accurately measured; however the results secured indicate molecular weights of considerable magnitude. Their molecular formula can usually be represented as  $(C_6H_{10}O_5)_x$ .

TABLE 31.—PHYSICAL CONSTANTS OF SOME DISACCHARIDES

Name	M.p.	[ $\alpha$ ] <sub>D</sub>	Phenyl- osazone, M.p.	Octaacetate	
				M.p.	[ $\alpha$ ] <sub>D</sub> (HCCl <sub>3</sub> )
Sucrose.....	170–86 dec.	+ 66.4		69	+ 59.6
$\alpha$ -Maltose.....	dec.	+168 (calcd.)	206	125	+122.4
$\beta$ -Maltose.....	160–5	+118		160	+ 62.7
Equil.-Maltose.....		+136			
$\alpha$ -Lactose.....	223	+ 90	200 dec.	152	+ 53.9
$\beta$ -Lactose.....	252	+ 35		90	– 4.3
Equil.-Lactose.....		+ 55.3			
$\alpha$ -Cellobiose.....	225 dec.	+ 24.4	208–10	229	+ 41
$\beta$ -Cellobiose.....		+ 16		202	– 14.6
Equil.-Cellobiose.....		+ 35			

TABLE 32.—RELATIVE SWEETNESS OF SUGARS (AND OTHER COMPOUNDS)

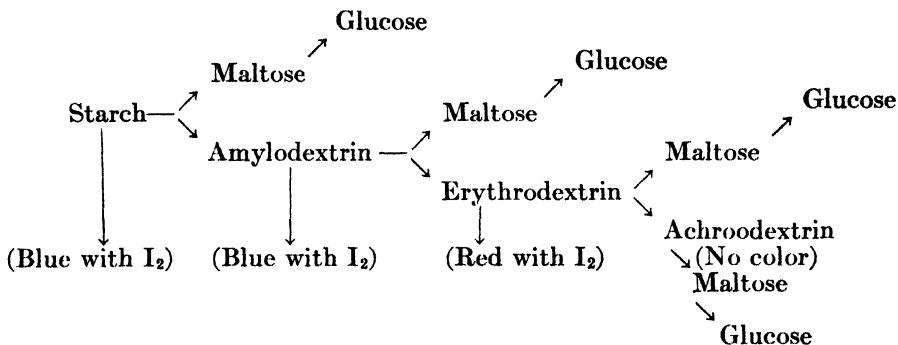
Fructose.....	173
Ethylene glycol.....	130
Invert sugar.....	130
Glycerol.....	108
Sucrose.....	100
Glucose.....	74
Mannitol ( <i>dl</i> ).....	57
Sorbitol ( <i>dl</i> ).....	54
Xylose.....	40
Maltose.....	32
Galactose.....	32
Lactose.....	16
Dulcin*.....	20000
Saccharin*.....	55000

\* Aromatic compounds, not related to sugars.

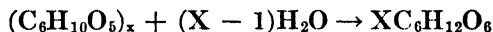
**Starch.** Starch occurs in distinct grains in the plants, mainly in seeds and tubers where it forms a reserve food supply. Starch granules from any one source have a characteristic form; this allows the use of the microscope to determine the source of a particular sample. Commercially starch is prepared from corn, potatoes, wheat, or rice.

Starch is insoluble in water, but on boiling the individual cell walls burst and a portion is dissolved, forming a milky solution called starch paste. This is used as a stiffening agent for cloth, as paste, etc. Raw starch or newly made starch paste gives a brilliant blue color with the slightest trace of iodine; on prolonged boiling of starch paste with mineral acids, it is progressively broken down to mixtures of simpler substances called dextrins. (When starch is hydrolyzed by diastase the hydrolysis product is maltose.) Dextrins are also made by heating dry starch to about 200°.

Starch does not reduce Fehling's solution and does not react with phenylhydrazine. It does not resinify when heated with alkali. Evidently no free carbonyl groups are present. Upon hydrolysis of starch the color obtained with iodine changes, with increasing degradation, from blue to various shades of red; finally no color is obtained with this reagent. It has been proposed that the hydrolysis liberates maltose units progressively, leaving a series of dextrans of lessening molecular weights as indicated in tabular form below.



The differing colors with iodine may or may not indicate the presence of definite dextrin compounds. The chemistry of the dextrans somewhat resembles that of the simple sugars; they have reducing properties and react with phenylhydrazine. The first distinct chemical compound produced by the hydrolysis of starch is maltose, and continued hydrolysis breaks this down into the final product glucose:



Both starch and the dextrans show the presence of OH groups in their reactions with acids to form esters. Nitrates and also acetates of starch are known and several find a commercial application as explosives and adhesives. Dextrans also function as adhesives; a common use is for the mucilage on postage stamps.

**Structure of Starch.** A tremendous amount of work has been done and is now going forward with the object of obtaining the structural formula for starch. Much has been learned but still more remains to be discovered. Starch occurs in two modifications, *alpha* amylose and *beta* amylose. The *alpha* amylose is an insoluble substance, found as the outer envelope of the starch grain. *Beta* amylose or granulose, which forms the bulk of the starch granules, is soluble. These may or may not be distinctly different chemical substances. Small amounts of the higher acids (palmitic, oleic, linoleic, linolenic) are found associated with *alpha* amylose in several starches, also phosphoric acid.

On the basis of the hydrolysis experiments which give a yield of maltose of the order of 80%, and in view of the isolation of molecules related to



maltose and having a small number of monosaccharide units, it has been suggested that starch is built up of maltose units united in glucoside formation.

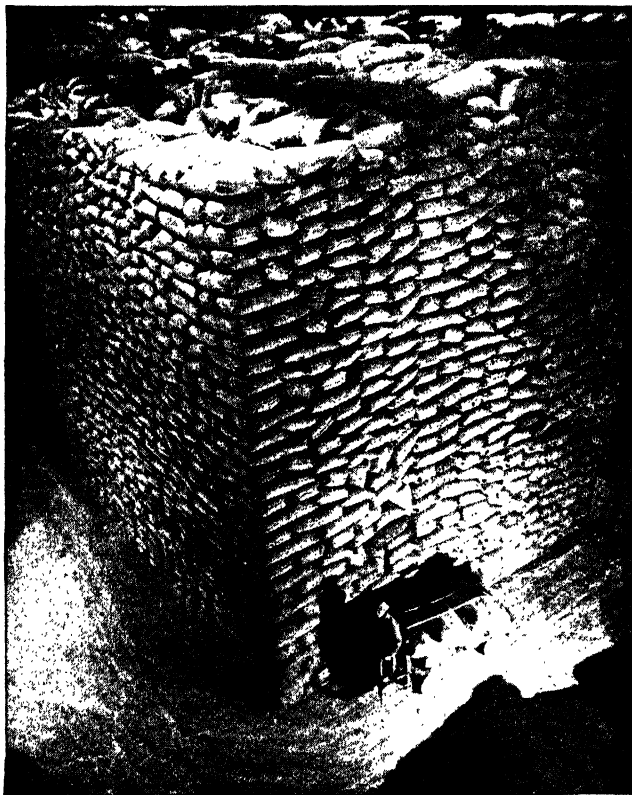
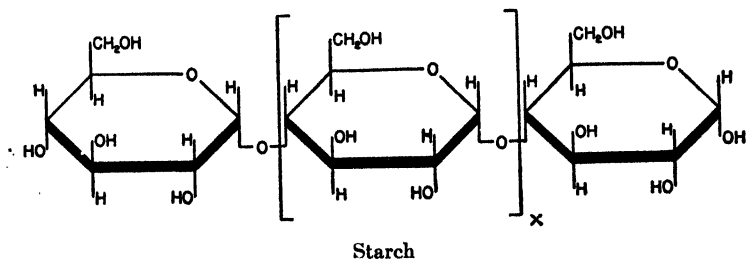


FIG. 60.—Raw sugar storage. (*Ind. and Eng. Chemistry.*)

tion. The molecular weight was set at about 5000 and the number (x) at about 22 to 28.



More recently the opinion has been expressed that the chains in the formula of starch under consideration contain from 100 to 700 glucose units. Another formula of starch is also proposed, in which from 500 to 2000 glucose units are involved, with branches at about every 25th glucose unit.

Inspection of the formula shows that branching could occur at the exposed #6 carbon atom of any glucose unit.

Starches are used as food, in laundry work, in medicine, in toilet articles, food preparations, candy; to make glucose, explosives, etc. Glucose is made (about one-half million tons a year) by hydrolysis of starch with dilute sulfuric acid.

**Glycogen, or Animal Starch** is formed in the liver and muscles as a reserve food supply which can quickly revert to glucose in emergency. Like starch it is a white powder, odorless and tasteless. With iodine it gives a red color. Its hydrolysis gives glucose. The molecular weight is about 2000 and a formula like that of starch has been proposed, (x) being 10. It is dextrorotatory. It does not reduce Fehling's solution.

**Inulin** is found in many plants. It is hydrolyzed to D-fructose. Its molecular weight is about 5000, and it is supposed to be made up of 30 fructofuranose rings in linear order (see starch structure). The compound is levorotatory. It does not reduce Fehling's solution. With iodine it gives a yellow color. Since fructose is sweeter than glucose there is much interest in the cultivation of the artichoke, from which inulin may be obtained. There is also the prospect of cheap power alcohol if artichoke cultivation proves successful at a low cost.

**Gums.** Gums are not true polyoses, but are built like glycosides. Hydrolysis yields xylose, arabinose, galactose. Gum acacia (gum arabic) is used in pharmaceutical work (tablet and pill making), also as an adhesive. Gum tragacanth is used as an emulsifier and adhesive.

**Mucilages.** Agar-agar is well known. Its hydrolysis gives galactose, possibly other sugars. As it is non-digestible, odorless, and tasteless, and has the property of swelling when placed in water, it is used to furnish "bulk" in treatment of constipation (Petrol-Agar, Agarol, Agarex).

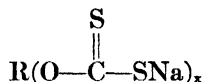
**Pectic Substances.** By "pectin" we mean a water-soluble substance, obtained commercially from apples or lemons, which with sugar and acids in proper ratio will set to a jelly. Certain fruits can form jellies without difficulty but others, deficient in pectin, cannot. In such cases commercial pectin may be used. The group includes "pectin" (water-soluble), and other substances which are water-insoluble. Much research has been devoted to the study of pectin, and not a little has been learned of the possible structural make-up. For lack of space this must be omitted. Pectin solutions have recently been used to promote growth of healthy tissue in wounds, while suppressing the growth of bacteria.

**Cellulose.** Cellulose is found in the framework of plants and in wood, and is thus very widely distributed in the vegetable kingdom. In wood the fibers of cellulose are cemented together by *lignins*, substances whose chemical nature is not yet known with certainty. Cotton wool is practically pure cellulose, as is linen which has been carefully washed. Cellulose, like starch, is a condensation product of glucose, for on prolonged treatment

with sulfuric acid, dextrins and finally glucose may be produced from it. Like starch and the sugars cellulose shows the properties of an alcohol, forming esters with both mineral and organic acids. Several of these will be referred to in a later paragraph.

**Chemical Reactions of Cellulose.** (1) Cellulose is soluble, apparently without much chemical change, in various rather unusual mixtures of reagents, such as:

- (a) Hydrochloric acid with zinc chloride.
- (b) Ammonium hydroxide with cupric hydroxide (Schweitzer's reagent).\*
- (c) Various "onium" compounds, both bases and salts (ethyl tributyl ammonium hydroxide).
- (2) Cellulose shows the behavior of an alcohol in the following reactions:
  - (a) Treated with sodium hydroxide and carbon disulfide, it forms a xanthate. Indicating the cellulose residue by R, the formula for a xanthate is:



It is also soluble in ethyl hydrogen xanthate.

- (b) In formation of cellulose esters (nitrates, acetates) it is noted that the "highest" esters obtainable have three acid groups to each six carbon atoms, hence the conclusion that there are three free OH groups for each glucose unit.
- (c) Cellulose forms ethers.
- (d) Sodium hydroxide of moderate strength yields sodium cellulose.

**Mercerization. Parchment Paper.** Treatment with strong alkali causes cellulose to swell and become somewhat translucent. The process of treating cotton with alkali to improve its appearance is called Mercerization after the name of its inventor, Mercer. Parchment paper is formed when pure cellulose sheets are momentarily treated with dilute sulfuric acid, washed and dried; the paper is tough and somewhat translucent.

(3) Oxidation of cellulose with nitric acid gives oxalic acid.

(4) When distilled destructively, cellulose gives acetone and acetic acid, CO<sub>2</sub>, CO, methane, ethylene, tar.

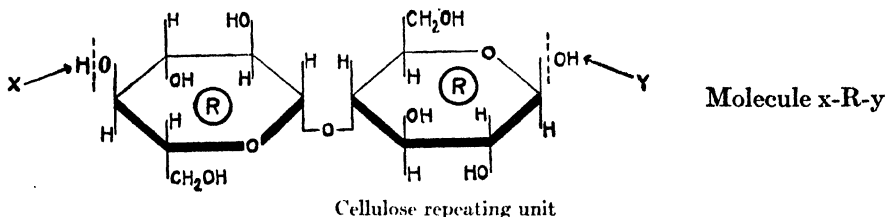
**Hemicelluloses.** These are found in various seeds like peas, coffee, and others. They are similar to cellulose, but when hydrolyzed several different hexoses and also pentoses are produced.

**Cellulose Structure.** Persistent research is being devoted to the problem of cellulose structure, but it presents great difficulties, due in part to the complexity of the molecule, and as well to the insoluble and intractable nature of the substance. According to present theory the cellulose molecule

\* Cellulose regenerated from such a solution is used as "Cuprammonium Rayon."

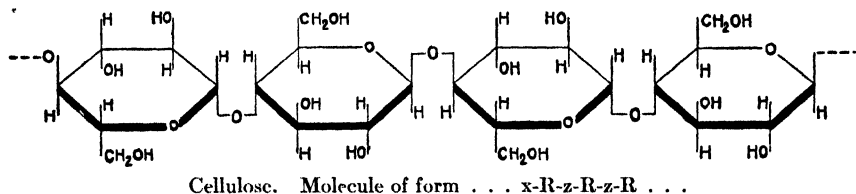
is a long chain formed from glucose (pyranose form) by loss of H and OH at the 1 and 4 positions respectively. Incomplete hydrolysis of cellulose gives cellobiose (page 375). This is a condensation product of  $\beta$ -glucose, whereas maltose, building unit of starch, is formed from  $\alpha$ -glucose. In other words, starch has  $\alpha$ -glucoside unions, cellulose has some  $\beta$ -glucoside unions.

Carothers has called attention to the ability of a compound of the type  $x\text{-R-y}$  ( $x$  and  $y$  are groups which can react with each other) to form a linear polymer of the type  $\dots x\text{-R-z-R-z-R} \dots$ . The "repeating unit" for cellulose would be:



that part of the above-pictured molecule lying between the dotted lines.

The formula for a portion of a cellulose molecule is then:



The length of chain varies with different molecules (100 to 200 hexose units, molecular weight 20,000 to 40,000),\* in other words we cannot assign a definite molecular formula to cellulose. The molecules lie side by side in a cotton fiber, being held laterally by residual valence forces. Considerable overlapping of molecules occurs, and if individual molecules have a length of at least 1000 Ångstrom units (molecular weight at least 12,000) a continuous fiber can be made from them.

## CELLULOSE DERIVATIVES

### Esters

**Cellulose Nitrates.** Several nitrates of cellulose are known, the extent of esterification depending upon the concentration of acid employed and time of its action. They are extremely combustible and, unlike cellulose,

\* Very much higher values of molecular weight are obtained by the use of the ultra-centrifuge. With this method values up to 500,000 have been obtained for purified cellulose. For description of the method, see references 10, 11, and 12 of the Protein Chapter.

are soluble in organic liquids such as alcohol and ether, from which they may be precipitated as a tough film.

Nitrates of cellulose are made by the action of mixed acid ( $\text{H}_2\text{SO}_4$  and  $\text{HNO}_3$ ) on purified cotton linters (fuzz which adheres to cotton seeds after passing through the cotton gin). Maximum esterification, three acid groups for each six carbon atoms, would yield a product with 14.17% nitrogen. The products obtained are not completely esterified and have a smaller percentage of nitrogen.

*Guncotton* (12–14% N) explodes too rapidly to be used as a propellant explosive (see page 201). To prepare it for such use in smokeless powder it is dispersed in an organic solvent (acetone, alcohol, ether) then extruded through dies to make perforated rods, from which the solvents are removed by evaporation. The rate of burning of the perforated pieces is a function of the surface exposed; this depends also to some extent on the character of the perforations.

*Cordite* is guncotton to which nitroglycerol, acetone, and vaseline have been added. A stabilizer (see page 461) is added to such explosives to prevent accumulation of deleterious nitrogen oxides which form in storage.

*Pyroxylin* (about 12% N). Pyroxylin burns more rapidly than untreated cotton, but is not explosive. It is dissolved in various solvents to form colloidal solutions which have a wide variety of uses.

*Lacquers*. In the familiar lacquers the pyroxylin is dispersed, together with pigments and plasticizers, in a mixture of organic solvents (esters, toluene, alcohols) which will evaporate at the proper rate to insure the setting of a firm elastic coat. Such lacquers are used for furniture, automobiles, interior woodwork. The lacquer coating of paper for wrapping purposes, especially for food products, gives the paper a better appearance, at the same time increasing its resistance to water, grease, and oil.

*Plastics*. Pyroxylin is blended with suitable plasticizers and coloring agents to obtain a product of the proper color and consistency. A mixture of the lower nitrates of cellulose with camphor is well known to the public under the name of celluloid. Pyralin is made from sheets of celluloid cemented under pressure, then cut across to give a striated appearance.

*Collodion* is pyroxylin in alcohol and ether. It is easily prepared as a laboratory exercise in the elementary course. It is a handy adhesive and coating substance, formerly much used to close small cuts and wounds.

*Artificial Leather*. Cloth is coated with a quick-drying pyroxylin lacquer, is dried, then run between rollers which impart to the surface the characteristic markings of the leather being imitated.

**Cellulose Acetate** is easily made by treating cellulose with acetic acid, acetic anhydride, and a little sulfuric acid (catalyst). It is a white solid, asbestos-like in appearance. Several acetates are recognized. Like the nitrates they are soluble in organic solvents, but are not explosive nor more combustible than untreated cellulose, in which respect they differ from the

nitrates. Cellulose acetates show greater stability to light and heat than the nitrates, with a smaller tendency to discolor on aging.

Cellulose acetate is capable of being spun into fine threads for the making of a silk-like cloth (Celanese). For this purpose it is dissolved in chloroform or other organic solvent, and the solution forced through fine openings into a chamber in which the solvent is quickly evaporated from the emerging filaments leaving them as hardened threads.

Cellulose acetate is also used for "safety film," as a molding material (resin) and (because it transmits ultraviolet light) as a substitute for glass in greenhouses. Another use is for the making of safety glass. Mixed esters of cellulose such as the nitroacetate combine the desirable features of acetates and nitrates. Several such esters are used.

**Cellulose Xanthate.** Purified wood pulp which has been changed to sodium cellulose by treatment with sodium hydroxide and aged, is treated with carbon disulfide to form cellulose xanthate (see page 380). Cellulose xanthate passes into solution as viscose upon treatment with sodium hydroxide solution. After a period of aging, the viscose is used to form threads or sheets. For Rayon making the solution is forced through fine holes in a die into a bath which regenerates the cellulose. Weaving and dyeing follow. In making Cellophane the viscose is forced through a narrow slit into the hydrolyzing bath where the cellulose is regenerated. Glycerol is incorporated for flexibility. Moisture-proof Cellophane is coated with a lacquer. Sausage casing is now being made by a process whose chemistry is similar to that for Cellophane. By trapping air in regenerated cellulose a series of cellulose bubbles may be formed; the invention has been given the name "Bubblfil." This material is to be used as replacement for kapok in cushions, life-rafts; as an insulator in sleeping bags. An indication of the increasing use of Cellophane is afforded by prices of the product.

Cellophane (per Pound)		Moisture-proof Cellophane (per Pound)	
1924.....	2.65	1927.....	1.60
1936.....	0.35	1936.....	0.46

### *Ethers*

The use of these compounds is relatively recent. For their production cellulose is treated with a base to form alkali cellulose which is next heated with an alkyl halide or alkyl sulfate. More recently ethers have been made by treating cellulose, dissolved in a tetraalkylammonium hydroxide, with a dialkyl sulfate or alkyl halide.

Ethyl cellulose and benzyl cellulose are well known. The former is soluble in many types of solvents and compatible with many plasticizers and resins. Uses for ethyl cellulose include paper sizing, adhesive use, use in printing inks, in certain soaps, in synthetic resins. Its chief advantage appears to be its solubility in cheap solvents (water, alcohol, toluene), its extensive compatibility and its stability to light, heat, and chemical action

by acids and bases. It has recently been introduced as a transparent wrapping material.

Any discussion of the direct uses of cellulose must not lose sight of its tremendous consumption in the form of clothing, rope, string, thread, wood, and (last but not the least of these), paper.

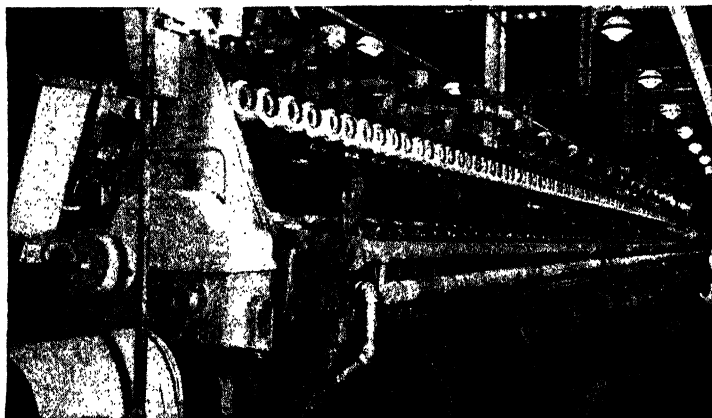


FIG. 61.—Viscose Rayon spinning machine. (*Du Pont Company.*)

Much effort has been expended to enhance the value of cotton, particularly for textile use. Chemical methods to improve appearance include treatment with copper oxide in ammonia, or with strong sulfuric acid.

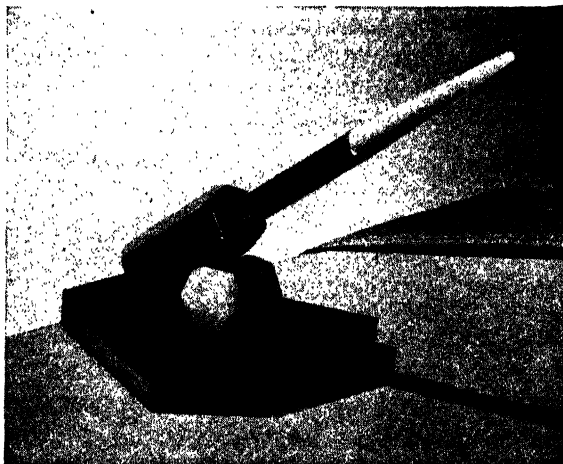


FIG. 62.—Desk stand with base of "Plastacele" cellulose acetate plastic and pen barrel of "Pyralin" cellulose nitrate plastic. (*Du Pont Company.*)

Finishes are applied by impregnating cotton with viscose or cellulose ethers, and then fixing the material on the cotton base by the usual regenerative treatments. Another development consists in impregnating cotton

with synthetic resins of the urea-formaldehyde type. Rayon impregnated with urea and formaldehyde solution, and then pressed between heated rollers while the resin forms, acquires a permanent wool-like texture. New uses for Rayon are found daily, and production is being increased as rapidly as possible to meet the enlarging demand. The 1938 production in this country was about 400,000,000 pounds. Much larger amounts are now in use.

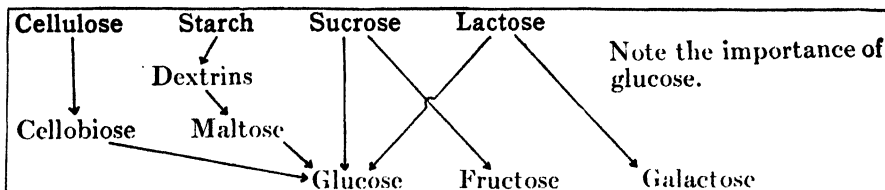


Chart of hydrolysis products.

## CARBOHYDRATE DATA (U.S.A.)

Annual corn grind.....	60 to 80 million bushels
Acres (40 bushels/acre).....	2,000,000 acres
Yield of starch.....	600,000,000 pounds
Yield of glucose.....	400,000,000 pounds
Yield of syrup.....	1,000,000,000 pounds
Dextrin, oil, other products.....	> 100,000,000 pounds

## RAYON DATA (1935) APPROXIMATE

Linters used.....	75,000,000 pounds
From acres, cotton.....	4,700,000 acres
Wood cellulose.....	175,000,000 pounds
Glucose.....	50,000,000 pounds
Rayon price, pound, 1924.....	\$2.00
1936.....	0.57

## INCREASE IN U.S.A. PRODUCTION, 1921-1940

Cotton.....	50 %
Wool.....	55 %
Silk (World).....	95 %
Rayon.....	over 3000 %

## HISTORICAL DATA

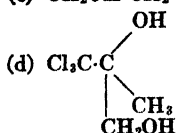
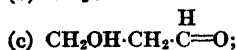
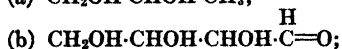
1660	Glucose from honey. Glauber.
1747	Discovery of sucrose and glucose in beets. Marggraf.
1791	Glucose from diabetic urine. Frank.
1811	Hydrolysis of starch to glucose. Kirchhoff.
1814	Iodine test for starch. Colin and Gaultier.
	Quantitative analysis of cane sugar. Berzelius.
1815	Reduction of copper salts by glucose. Vogel.
	Biot notes optical activity of sucrose.
	Fermentation of glucose. Gay-Lussac.
1817	Glucose optically active. Biot.
1819	Glucose from cellulose. Gay-Lussac.
	Maltose from hydrolysis of starch. De Saussure.



- 1828 Quantitative analysis of glucose. De Saussure.  
 1833 Dextrin from starches. Biot and Persoz.  
 1846 Mutarotation of glucose. Dubrunfaut.  
 1847 Maltose from enzymatic hydrolysis of starch. Dubrunfaut.  
 1849 Fehling's solution.  
 1856 Isolation of galactose. Pasteur.  
 1861 Formose from formaldehyde. Butlerow.  
 1863 Glucose an aldehyde-alcohol. Berthelot.  
 1864 Baeyer formaldehyde theory.  
 1868 Celluloid. Hyatt.  
 1872 Synthesis of glycerol from acetic acid. Friedel and Silva.  
 1875 Phenylhydrazine. E. Fischer.  
 1883 Ring formulas for sugars proposed. Tollens.  
 1884. First synthetic fiber. (Nitrocellulose) Chardonnet.  
 1885 Kiliani reaction.  
 1885-1894 Important work by E. Fischer.  
 1887 Acrose synthesis. Fischer and Tafel.  
 Osazone reaction. Fischer.  
 Arabinose proved a pentose. Kiliani.  
 Mannose from mannitol. Fischer.  
 1889 Xylose recognized as a pentose. Wheeler and Tollens.  
 1890 Isomaltose synthesis. Fischer.  
 Synthesis of glucose. Fischer.  
 Mannose and fructose synthesis. Fischer.  
 1893 Methyl glucosides. Fischer.  
 1895 Lobry de Bruyn transformation.  
 1903 Hydrolysis of methyl glucosides to glucoses. Armstrong.  
 Methylation of sugars. Purdie and Irvine.  
 1907 Alkaline oxidation of glucose. Nef.  
 1915 Methylation of sugars. Haworth.  
 1916-19 Work by Fischer.  
 1917 Cellulose acetate fiber.  
 1923 Structures of monosaccharides. Haworth, Hirst, Irvine.  
 1925- Studies of carbohydrate oxidation. Evans.  
 1927 Synthesis of maltose. Pictét.  
 1942 Synthesis of lactose. Hudson.  
 1942 Synthesis of cellobiose. Hudson.  
 See also the historical list in the Appendix, p. 800.

### REVIEW QUESTIONS

1. Draw projection formulas similar to those on page 337 for  $\alpha$ -aminopropionic acid; for 2,3-dibromobutane. How many isomers could exist for the latter compound?
2. Indicate the asymmetric carbon atoms (if any exist) in the following compounds:



3. Summarize in the form of a chart or table the behavior of the following compounds (Starch, Lactose, Maltose, Sucrose, Glucose, Fructose) with regard to: (a) taste; (b) solubility in water; (c) action as a reducing agent; (d) products of hydrolysis; (e) fermentation.
4. Show by equations how an aldohexose may be formed from arabinose.
5. Write equations showing (a) the change of arabinose to an aldotetrose; (b) to a ketohexose.
6. Write a set of equations showing how: (a) glucose may be converted to fructose; (b) glucose may be formed from fructose.
7. What chemical reactions prove the presence of OH groups in starch?
8. By what properties and tests could the following compounds be distinguished from each other:
  - (a) sucrose and glucose?
  - (b) sucrose and maltose?
  - (c) glucose and fructose?
9. What was the early significance of the term "carbohydrate"? What is its present significance?
10. Give in tabular form the scheme of classification of the carbohydrates; include a graphic formula for an example of each type of sugar in the table.
11. Review the proof of the structure of glucose (omitting that part having to do with the assignment of space positions to H and OH).
12. Give the proof of the structure of fructose, except that part which deals with the space position of H and OH.
13. What is a glucoside? How do we explain the existence of the *alpha* and *beta* glucosides?
14. List the esters of cellulose which find commercial uses; make an exhaustive list of such applications.
15. An aldohexose and ketohexose form an identical osazone. What inference may one draw from this fact?
16. When two aldohexoses form an identical osazone, what is the relationship between them? How may one be converted to the other?
17. How may one make gulose from xylose?
18. Why is it more desirable to use the prefixes D and L to show relationships of sugars than to show the actual optical rotation?
19. Explain the meaning of the following letters when prefixed to the name of a sugar. (a) *d*-; (b) D-; (c) D(+)-; (d) L(+)-; (e) *dl*-.
20. Look up in a biochemistry text the composition of Benedict's solution and Barfoed's solution. Which of the three, Fehling, Barfoed, or Benedict, should cause the most profound changes (fragmentation) in glucose?
21. Write formulas for:  $\beta$ -furanose form of glucose;  $\alpha$ -pyranose form.
22. Suppose you had isolated a new aldehyde monosaccharide from a plant called *fragaria vesca*. What would you call it? Outline the research which would be needed to classify it among the sugars and learn its formula.
23. Write projection formulas for the following sugars: L-mannose, L-arabinose, L-galactose, L-lyxose.
24. What aldoses are epimeric with the following: mannose, ribose, idose, allose?
25. Explain why it is possible for all carbohydrates to give the Molisch test.
26. Name four separate industries whose chief raw material is carbohydrate.
27. Account for the fact that glucose is a stronger acid than hexyl alcohol.
28. Trace the possible change of glucose to fructose in a plant. Is the change quantitative?
29. What evidence have we that monosaccharides exist in ring forms?
30. Write projection formulas for  $\alpha$  and  $\beta$ -methyl glucofuranosides; of tetramethyl- $\alpha$ -methyl glucopyranoside and its hydrolysis product, tetramethylglucopyranose.
31. The synthesis of glycerol from carbon is indicated on page 364. Write complete equations for the steps shown.

32. Show an aldol condensation between glyceraldehyde and dihydroxyacetone, which yields fructose.
33. Indicate by the use of a graphic formula how it is possible for a reducing disaccharide to form a glycoside.
34. Can a non-reducing disaccharide display mutarotation? Why?
35. Show by the use of the graphic formula why sucrose cannot form a glycoside.
36. Name six men who have made contributions to the chemistry of sugars. Name contributions by Emil Fischer.
37. Glucose and fructose give an identical osazone. Use this fact to show that the carbonyl group is at number two position in the fructose chain.
38. Mild oxidation of glucose yields an acid with six carbons and twelve hydrogens. Use this fact to prove that the oxidation affected an aldehyde group and not a primary alcohol group.
39. Discuss the preparation and uses of: (a) Cellulose acetate; (b) Pyroxylin; (c) Celluloid; (d) Collodion; (e) Caramel.
40. Give uses of the following reagents in connection with carbohydrate chemistry. (a) Nitric acid; (b) Phenylhydrazine; (c) Fehling solution; (d) HCN; (e) Acetic anhydride; (f) Carbon disulfide and sodium hydroxide.

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**PART II**  
**AROMATIC COMPOUNDS**



## CHAPTER XX

### AROMATIC HYDROCARBONS

**Introduction.** The substances considered up to this point in our study belong to the group called aliphatic compounds. This name, derived from a Greek word signifying fat, was given to the group as a whole, because the fats and fatty acids of this group were among its first members to receive careful study; likewise the fats formed the source from which a number of the derivatives of this group could be prepared.

At the time we are considering, organic chemists were aware of another class of compounds, mainly of vegetable origin, whose members showed different properties from those associated with aliphatic substances. Due to the pleasant odors of many of these (oil of wintergreen, bitter almond oil, turpentine, etc.) they were known as aromatic compounds, a name which has been retained, although not with its original significance, for we now know of many aromatic compounds which are practically odorless, while on the contrary a number of the aliphatic series (among the esters, aldehydes, etc.) have fragrant and pleasant odors.

The chief distinction between the two series is a structural one; the aliphatic compounds possess an open-chain structure, while we shall find that the aromatic compounds have ring structures (closed chains). See footnote, page 409.

Some ring compounds have already received attention, among them cyclic anhydrides, lactones, sugars, etc. Such examples differ from the true aromatic compounds in that their rings are easily broken and reformed. They lack the stability of structure which belongs to the aromatic compounds.

**Importance of Benzene.** As methane forms the parent substance from which the aliphatic series may be derived, so we shall note a similar relationship between aromatic compounds and the substance Benzene, whose molecular formula is  $C_6H_6$ . This was first shown when the aromatic compounds were oxidized or otherwise broken into simpler substances. Benzene,  $C_6H_6$ , Picric acid,  $C_6H_2(NO_2)_3(OH)$ , and other compounds having six or more carbon atoms were thus produced. Further chemical action was either without any result, or it produced a complete breakdown, yielding carbon dioxide, water, etc. Kekulé embodied these results as follows: "The simplest aromatic substances contain at least six atoms of carbon." The strategic importance of benzene as the nucleus of the aromatic compounds was established by this early work and has been confirmed by later experimentation. Benzene itself was isolated from oil gas in 1825 by Fara-



day, and in 1842 it was found in coal tar by Leigh. (Separation from coal tar, 1845, Hofmann.)

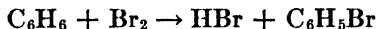
### STRUCTURE OF BENZENE

Any effort to place benzene among the aliphatic compounds is checked at once upon consideration of its chemical properties. Its formula,  $C_6H_6$  (type formula  $C_nH_{2n-6}$ ), indicates great unsaturation in case we assume an open-chain arrangement of its carbon atoms. The following formulas might be tentatively assigned:



however, none of these will answer as a formula for benzene, because each of them indicates a compound which is easily oxidized and which will readily add such reagents as bromine, hydrogen iodide, or hydrogen chloride. Benzene, on the contrary, resists oxidation to a marked degree; moreover it adds halogens only under special conditions, and does not react with hydrogen iodide, hypochlorous acid, and other agents easily taken up by aliphatic unsaturated compounds.

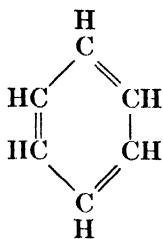
Benzene reacts with chlorine or bromine by substitution, as would be true of a saturated aliphatic hydrocarbon:



It is notable that one and only one monosubstitution product may thus be formed. No matter how the reaction is carried out, one and the same monobromobenzene results. This goes to show that all six hydrogens of benzene are equivalent. Either (1) or (3) of the tentative formulas given above would allow more than one monosubstitution product. A substance answering to formula (1) has been found. It is dipropargyl, a compound entirely dissimilar to benzene. Dipropargyl behaves in accord with its structural formula, being easily oxidized, and adding bromine readily to form  $C_6H_6Br_8$ . When benzene adds bromine the compound  $C_6H_6Br_6$  is formed. If benzene had an aliphatic structure it should form  $C_6H_6Br_8$  when saturated with bromine.

**Kekulé Formula.** In 1865, Kekulé proposed a ring structure for benzene as shown at the top of p. 395. The six carbons are shown united to form a hexagon. Each carbon bears one hydrogen atom, and is joined to neighboring carbon atoms by alternate single and double bonds.

This formula satisfies the experimental fact that *only one form is known for any monosubstitution product of benzene*, in that it shows all the hydrogen atoms as equivalent. Another experimental finding is likewise predicted by this formula, namely, *disubstitution products of benzene exist in three forms*.



Kekulé formula

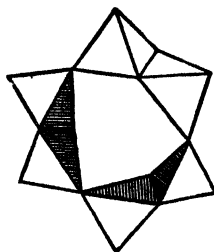
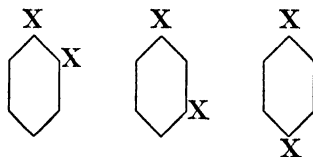


FIG. 63.—Space model of Kekulé formula.

For if we let X represent a certain group substituted for hydrogen of benzene, the following graphs show that three different structural forms are possible:



Many years of laboratory work with benzene have failed to show any instance in which more than three forms of a disubstitution product of benzene have been prepared.

Objections to the formula of Kekulé center about its possession of double bonds. Facts drawn from a study of aliphatic compounds argue that such a structure predicts reactions of the olefin type; therefore other structures have been proposed which seek to avoid this difficulty. Among these are the following:

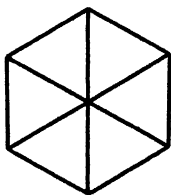


FIG. 64.—Diagonal formula of Claus, 1867.

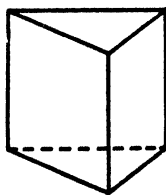


FIG. 65.—Prism formula of Ladenburg, 1869.

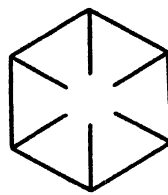


FIG. 66.—Centric formula of Armstrong and Baeyer, 1892.

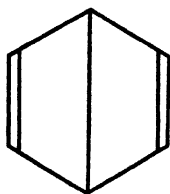


FIG. 67.—Para bond formula of Dewar, 1867.

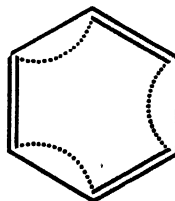
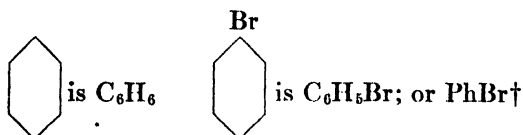


FIG. 68.—Conjugated formula of Thiele, 1899.

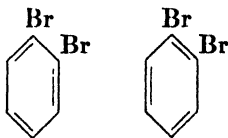
Notwithstanding the value which certain of these formulas possess,\* the Kekulé formula is generally accepted and used by chemists. It is ordinarily written without printing the carbon and hydrogen atoms or indicating the double bonds, i.e., when the hexagon alone is printed,  $C_6H_6$  is understood, while if another atom than hydrogen appears at any point, this indicates that the corresponding hydrogen has been substituted by the atom shown in its place. The formulas below will make this clear.



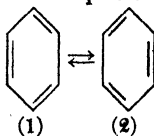
For the most part we shall print the symbol  $C_6H_6$  to represent the benzene ring, as it takes much less room than the ring. Where needed, for the sake of clearness, the ring will be used.

The student will see that we are justified in our use of the abbreviated formula for benzene, because of the great stability of the ring. In most of the reactions to be studied, the ring itself is absolutely unchanged. Therefore it becomes a matter of indifference whether or not the formula used accurately shows every particularity of structure, and time is saved by simplification.

**Further Objections to Kekulé Formula.** Objections have been raised to the Kekulé formula for benzene because it predicts the existence of benzene derivatives which have never been discovered. For instance, two compounds like the following should exist:



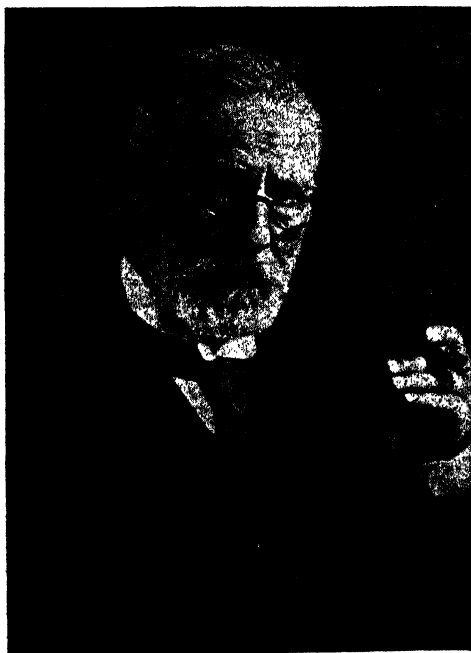
differing from each other in that in one compound a double bond joins the carbons holding the bromine atoms, while the other compound has a single bond at this point. No such isomers had ever been made. Kekulé countered this objection by stating that the double bonds are not static, but are in continual oscillation between the two positions shown in (1) and (2) below:



\* The student should understand that the "benzene problem" is not yet solved. New proposed structures appear periodically and the total literature bearing on this subject is immense.

† The Greek letter  $\phi$  is sometimes used to represent the  $C_6H_5$  (Phenyl) group. Ph has the same significance.

JACOBUS H. VAN'T HOFF. (1852-1911, Dutch.) Best known for his stereochemical theory and his work in physical chemistry. He was a Nobel prizewinner in 1901. See *J. Soc. Chem. Ind.*, **30**, 405 (1911), *J. Chem. Education*, **11**, 355 (1934); *J. Chem. Soc. (London)*, **103**, 1127 (1913), Harrow, pp. 79, 337; also this book, page 333.



PAUL EHRLICH. (1854-1915, German.) Ehrlich coined the word chemotherapy for the selective action of chemicals on germs. He pioneered in this study, producing among other curative compounds. Trypan blue for sleeping sickness and salvarsan for syphilis. He received the Nobel prize in 1908. See *J. Soc. Chem. Ind.*, **34**, 893 (1915); also this book, page 603.

The Armstrong and Baeyer formula would represent a transient condition during this oscillation.

This oscillation theory does not, however, tell us why benzene behaves as a saturated compound; the formula of Thiele attempts to explain this, in calling attention to the fact that benzene has conjugated double bonds

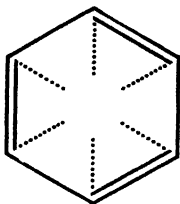


FIG. 69.—Structure of benzene showing conjugated double bonds and partial valence.

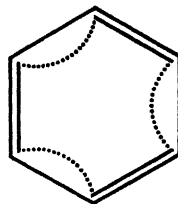
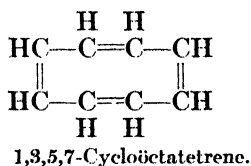


FIG. 70.—Partial valence neutralized.

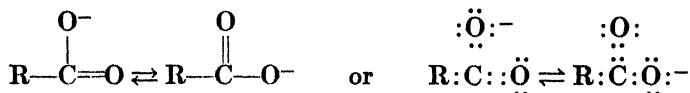
(page 62). The partial valence of the alternate carbons is presumed to be neutralized in benzene just as in other systems of conjugated double bonds. Since the free partial valence disappears on such neutralization, benzene should not behave like an ethylene compound.

This explanation is not entirely adequate. It predicts that other ring hydrocarbons with alternate single and double bonds (conjugated) would behave like benzene. Willstätter announced in 1911 the preparation of cycloöctatetrene, to which he assigned the following structure. This substance behaves like a highly unsaturated compound. If we could be sure of the formula given here, it might be possible to use this chemical evidence. However Hurd (1939) has challenged the reliability of this formula and it can no longer be accepted as correct.



It is now believed that the stability of benzene is accounted for by the fact that the molecule displays resonance.

**Resonance.** There are many organic compounds for which two or more graphic formulas can be constructed, which are practically equivalent so far as concerns the positions of the constituent atoms, differing from each other only in the electron distribution. An acid ion may be taken as an example:



Here the only difference between the two structures has to do with the

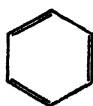
possession of the double bond by alternate oxygen atoms. A system of this kind will exhibit resonance; its actual structure is not that indicated by any one of the graphic formulas mentioned, but partakes of the nature of each of them. If a formula could be drawn it would indicate that the molecule has a form intermediate between those shown by the several graphic formulas.

Resonance and tautomerism are to be carefully distinguished from each other. Tautomerism implies the simultaneous existence of two molecular forms in equilibrium with each other. Cases are known in which each form may be isolated. In case of resonance only one molecular form exists, and this differs from the possible forms which correspond to ordinary graphic formulas solely in the placement of the electrons and in the distances between certain atoms.

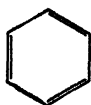
There are several consequences from the resonance: (1) the molecule is more stable than would be expected from inspection of the ordinary graphic formula. For example, aldehydes and ketones are not hard to reduce, but acetic acid, which also has a carbonyl group, is difficult to reduce. (2) In a resonating molecule the distance between atoms is lessened. If a C—C union resonates between single and double bond, the C—C distance is less than that normal for a single bond and will approach that spacing which is normal for a double bond. Since the measurement of interatomic distances has become possible, it can be told whether resonance is taking place in a given molecule. The C—C distance in benzene is  $1.39\text{\AA}$ , while the normal C—C distance is  $1.54\text{\AA}$ . The spacing for a double bond is  $1.32\text{\AA}$  (see page 69). The  $1.39\text{\AA}$  spacing in benzene therefore indicates that the bonds are intermediate in character between double and single bonds.

As stated above, a resonating molecule is found to have less energy than would be calculated for any one of its resonating structures. This difference in energy is the **resonance energy**; for benzene the value is 39 Cal. per mole. The heat of formation of benzene is 39 Cal. greater than would be calculated for the Kekulé structure. This figure indicates the stabilization of the molecule consequent upon the resonance.

The resonance of benzene is assumed to occur principally between the two forms (I) and (II):



(I)  
FIG. 71.



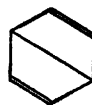
(II)  
FIG. 72.



(III)  
FIG. 73.



(IV)  
FIG. 74.



(V)  
FIG. 75.

There may also, perhaps, be a resonance between the three possible Dewar forms, (III), (IV), and (V).

## PROPERTIES OF BENZENE

Benzene is a clear, colorless liquid having a peculiar not unpleasant odor. It freezes at  $5.5^{\circ}$  and boils at  $80.1^{\circ}$ . Its density, like that of the other liquid hydrocarbons, is less than 1 (0.878 at  $20^{\circ}\text{C}.$ ). Benzene is insoluble in water, but readily dissolves in alcohol or ether. It burns with a sooty yellow flame. Benzene vapor forms an explosive mixture with air, and the compound may be used in internal combustion engines. It has high antiknock value (see page 42). Benzene is a good solvent for fats and waxes, also for resins.

## COMMERCIAL SOURCE OF BENZENE

Benzene is commercially obtained from coke oven gas and from coal tar, both of them products of the destructive distillation of coal. Three types of products result when coal is heated out of contact with air: gaseous, liquid, and solid. The gases comprise coal gas (hydrogen, methane, carbon monoxide), ammonia; also carbon dioxide, ethylene, acetylene, etc. These gases leave the hot coke oven, together with the condensable vapors of water and low molecular weight aromatic hydrocarbons.

The gas mixture is cooled and scrubbed to remove tar and ammonia liquor, and is then stripped of its content of aromatic compounds. These form the "light oil."

The light oil, boiling from  $80^{\circ}$  to  $200^{\circ}$ , contains benzene and toluene, also phenol, pyridine, and thiophene; these latter substances are removed by chemical treatment. Further fractional distillation effects a separation of the benzene from the toluene, xylenes, and other hydrocarbons of the light oil.

Coal tar is an oily viscous complex mixture of aromatic organic compounds. Its distillation yields, in the lower fractions, small amounts of benzene, toluene, and xylenes. Much larger yields of these "light oil" components are obtained from the coke oven gas.

Higher boiling fractions of coal tar contain the xylenes, mesitylene, ethylbenzene, naphthalene, anthracene, phenol, cresol, phenanthrene, and other substances both liquid and solid, which are derivatives of benzene, and as such will receive attention in ensuing pages. Coke is the solid residue of the distillation of coal, while pitch comprises the residue of coal tar distillation.\*

About 500,000,000 gallons of coal tar were distilled in this country in 1939; about 10,000,000 gallons of tar were exported. A large percentage of the coal tar is represented by pitch and creosote oil. The latter is used for the preservation of wood, pitch for roofing and as a constituent of road-making material. About 125,000,000 gallons of creosote oil per year are used in this country.

\* For details of coal tar distillation, see References 2, 3, and 5 at the end of this chapter.

**History of Coal Tar Industry.** Coal tar first came to public notice with the use of coal gas for illumination (about 1810). There was no particular use for the tar and it was usually burned for fuel. Later uses included the preservation of timber with creosote oil, the production of lamp black, and sundry employments of the volatile distillates as solvents.

About 1850, chemists began investigation of the nature of coal tar. A number of discoveries of great importance to aromatic chemistry quickly followed. After the publication of the Kekulé benzene formula, research proceeded more surely and more quickly. New medicinals, new types of dyes, new explosives, new coatings, other novel developments came from this work (see historical table, page 800).

Today electricity has largely supplanted gas for illuminating purposes. However the distillation of coal is practiced on a wider scale than ever because the coke so obtained is needed in the steel industry. Coal distillation yields large amounts of gas and coke and much smaller amounts of products from which we obtain aromatic chemicals (coal tar and light oil). The following table shows the average yield from a ton of bituminous coal.

#### DISTILLATION PRODUCTS FROM ONE TON OF COAL

Coke.....	1500 pounds
Gas.....	11,000 cu. ft.
Coal tar .....	10 gal.
Ammonium sulfate.....	25 pounds
Light oil.....	3.5 gal.

Hundreds of millions of tons of coal are burned annually without any recovery of by-products; other millions of tons are converted to coke in beehive ovens which do not save the by-products. Nevertheless an enormous amount of coal is coked in the by-product coke ovens, thus assuring the chemical industry an ample supply of aromatic crudes at low prices. Small amounts of benzene, toluene, and xylenes occur in most petroleum; however an almost inexhaustible source of aromatic hydrocarbons is now offered through the cyclization of aliphatic hydrocarbons (see page 405).

#### COAL DISTILLATION DATA (U.S., 1941)

Coal distilled.....	82,608,837 tons
Products:	
Coke.....	58,482,422 tons
Coal tar.....	704,149,468 gal.
Gas.....	892,819,811 M. cu. ft.
Ammonium sulfate.....	870,752 tons
Light oil.....	174,000,000 gal.*
Naphthalene.....	83,810,422 pounds

\* Estimated.

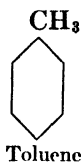
#### PRINCIPAL COAL TAR CRUDES, 1939 PRICES

Benzene, gal.....	\$0.14
Toluene, gal.....	0.20
Xylene, gal.....	0.23
Naphthalene, pound.....	0.02
Anthracene, pound (retail).....	0.70

### HOMOLOGS OF BENZENE

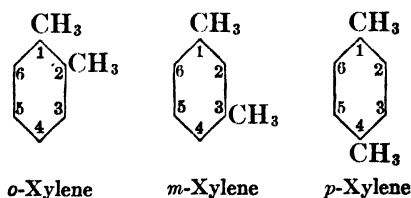
Homologs in the aromatic series of compounds differ from each other by the increment  $\text{CH}_2$  as in the aliphatic group. Thus, the substance next to benzene in the series is  $\text{C}_7\text{H}_8$ . This is known as methylbenzene or toluene:





The methyl group is called a "side-chain," this term being reserved for any group substituted for hydrogen of an aromatic ring, except such very simple units as Cl, OH, etc. The ring itself is spoken of as the "nucleus" of the compound. Side-chains are ordinarily placed at the top of the ring (see above) or at the right hand. The student must understand, however, that the formula for a monosubstitution product of benzene may show the substituting group at any corner of the ring, since all hydrogens of benzene are equivalent.

There is, of course, but one methylbenzene; monosubstitution products of benzene exist in one form only, as already stated. Dimethylbenzene, however, exists in three isomeric forms; these compounds are known as xylenes.

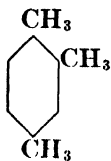


As a preliminary to naming these compounds, it is convenient to number the corners of the benzene ring from 1 to 6 as shown in the figures. The three xylenes may then be called 1,2-dimethylbenzene, 1,3-dimethylbenzene, and 1,4-dimethylbenzene.

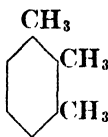
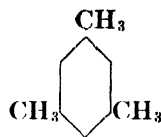
Groups situated on adjacent carbons of a benzene ring are said to be *ortho* to each other, those separated by one carbon of the nucleus are called *meta* to each other, while two groups separated by two carbons of the ring are *para* to each other (these names are commonly represented by the letters *o*, *m*, and *p*). Thus, we may name the three xylenes *o*-xylene, *m*-xylene, and *p*-xylene. The type of isomerism shown by the xylenes is called *position isomerism*. The groups have been placed here so as to use the lowest numbers possible on the ring. However they would still be in *ortho* position to each other if placed on carbons 2-3 or 5-6, and in *meta* position if placed on carbons 2-4 or 4-6.

Isomeric with the xylenes is ethylbenzene,  $C_6H_5 \cdot C_2H_5$ . This substance occurs in coal tar together with the xylenes and toluene.

When three like groups are substituted for hydrogen in benzene, the number of possible isomers is three; the three trimethyl benzenes may be shown to illustrate this point.

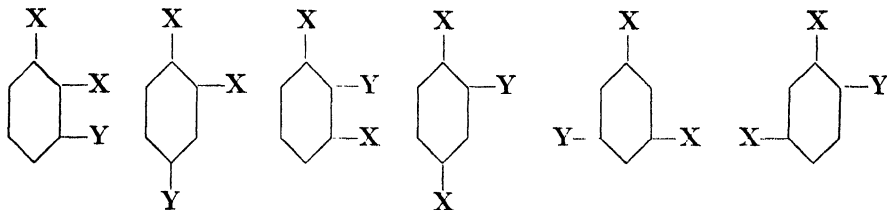


1,2,4-compound

1,2,3-compound  
Trimethyl benzenes

1,3,5-compound

If three groups are substituted, of which two only are alike, six isomers are possible:

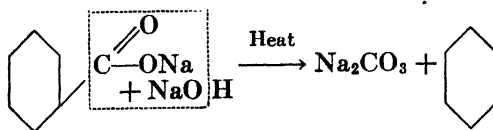


If all three groups are different, ten isomers exist.\* These examples show that the possibilities for isomerism are very great in the aromatic series. Strong support for the Kekulé structure is afforded by the fact that the number of isomers prepared in any case has never exceeded the number predicted by the formula. The accompanying table lists the formulas, boiling points, melting points, and densities of a number of the simpler aromatic hydrocarbons.

### PREPARATION OF BENZENE

The methods of preparation given here have a theoretical rather than a practical interest, although methods (1) and (2) give reasonable yields and may be employed when a pure product is desired. Benzene obtained from coal tar contains thiophene, a sulfur compound which requires chemical treatment for its removal; also it is apt to contain a certain proportion of toluene.

(1) Preparation of benzene by "heating the dry sodium salt of the acid having one more carbon, with excess of a strong base" (anhydrous). This is a method used to obtain the aliphatic saturated hydrocarbons.

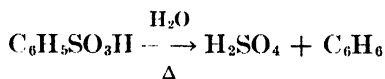


\* It is advisable for the student to check these statements by actual trial with pencil and paper.

TABLE 33.—PHYSICAL CONSTANTS OF SOME AROMATIC HYDROCARBONS

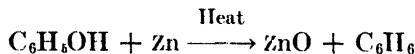
Name	Formula	M.p., °C.	B.p., °C.	Sp. g., 20°/4°	Ht. of comb.
Benzene	C <sub>6</sub> H <sub>6</sub>	5.5	80.1	0.878	782.3
Toluene	C <sub>6</sub> H <sub>5</sub> CH <sub>3</sub>	— 95	110.8	0.866	934.2
Xylene ( <i>o</i> )	C <sub>6</sub> H <sub>4</sub> (CH <sub>3</sub> ) <sub>2</sub>	— 25	144	0.881	1091.7
Xylene ( <i>m</i> )		— 47.4	139.3	0.865	1089.0
Xylene ( <i>p</i> )		+ 13.2	138.5	0.861	1089.1
Hemimellitene	1,2,3-C <sub>6</sub> H <sub>3</sub> (CH <sub>3</sub> ) <sub>3</sub>	— 25.5	176.1	0.895	
Mesitylene	1,3,5-	— 44.8	164.8	0.863	1243.6
Pseudocumene	1,2,4-	— 44.1	169.3	0.876	1241.7
Ethylbenzene	C <sub>6</sub> H <sub>5</sub> C <sub>2</sub> H <sub>5</sub>	— 94.4	136.2	0.868	1091.2
Ethyltoluene ( <i>o</i> )	CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> C <sub>2</sub> H <sub>5</sub>	<— 17	164.9	0.882	
Ethyltoluene ( <i>m</i> )			158.9	0.869	
Ethyltoluene ( <i>p</i> )		<— 20	162	0.862	
Propylbenzene ( <i>n</i> )	C <sub>6</sub> H <sub>5</sub> C <sub>3</sub> H <sub>7</sub>	— 99.4	159.5	0.862	1246.4
Prehnitene	1,2,3,4-C <sub>6</sub> H <sub>2</sub> (CH <sub>3</sub> ) <sub>4</sub>	— 4	204	0.901	
Isodurene	1,2,3,5-	— 24	195–7	0.896 <sup>00</sup>	
Durene	1,2,4,5-	+ 79–80	193–5	0.838 <sup>810</sup>	1393.6
Pentamethylbenzene	C <sub>6</sub> H(CH <sub>3</sub> ) <sub>5</sub>	53	230–1	0.847 <sup>1070</sup>	
Hexamethylbenzene	C <sub>6</sub> (CH <sub>3</sub> ) <sub>6</sub>	166	265	.....	1711.9

(2) Preparation by treatment of a sulfonic acid with steam:

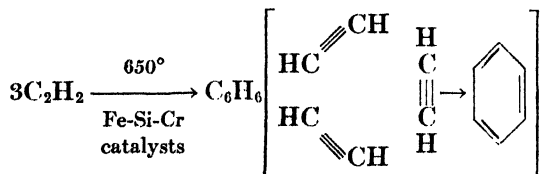


Sulfonic acids are discussed in a later chapter.

(3) The reduction of phenol (carbolic acid) yields benzene. This may be carried out by heating with zinc dust.



(4) Benzene may also be made in good yield by the polymerization of acetylene, caused by passing the gas through a red-hot tube:

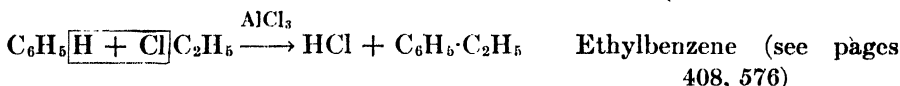


This method of formation is important as it shows a transition from the aliphatic to the aromatic series. The reaction also supports the contention that there are three double bonds in benzene. Many other aliphatic hydrocarbons yield benzene or an alkyl benzene when subjected to pyrolysis; for example, hexane passed over Cr<sub>2</sub>O<sub>3</sub> at 470° gives a 17% yield of benzene;

octane gives 63 % of *o*-xylene; *n*-heptane gives 90 % of toluene (see Reference 34, page 426). The hydroforming process noted on page 42 produces aromatic hydrocarbons, including toluene and xylenes. These existing methods of cyclization were expected to furnish 70,000,000 gallons of toluene for the year 1942.

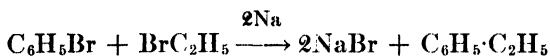
#### PREPARATION OF BENZENE HOMOLOGS

(1) Homologs with a single side-chain may be prepared by the Friedel and Crafts reaction. This is carried out by the use of an alkyl halide corresponding to the desired alkyl group, together with benzene; aluminum chloride is the catalyst.

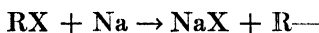


The Friedel and Crafts reaction is taken up in detail in Chapter XXIX.

(2) The Wurtz-Fittig reaction\* employs a halogen derivative of benzene, together with the proper alkyl halide and an active metal, such as sodium or zinc:



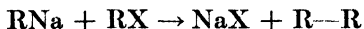
One explanation of the Wurtz reaction states that we have first a reaction between the halogen compound and metal to form a free radical and metal halide:



The free radical can undergo several different reactions, but we are interested in its reaction with additional metal to form an organometallic compound:



In the second phase of the reaction, the organometallic compound reacts with additional halogen compound:



In the formation of ethylbenzene there are, of course, two RNa compounds. Thus in the second phase of the reaction we may obtain butane, biphenyl, or ethylbenzene. The yield of biphenyl is small because phenylsodium reacts more readily with ethyl bromide than with phenyl bromide. Also phenyl bromide reacts more rapidly with sodium than does ethyl bromide; this cuts down the yield of butane. The free radical mechanism of the Wurtz reaction is not upheld by the most recent research (see Reference 5, page 436); it may soon be necessary to abandon this conception.

\* Ordinarily no distinction is made between the Wurtz (aliphatic) and the Fittig (aromatic) synthesis. It is called Wurtz-Fittig whether applied to aliphatic or aromatic compounds.

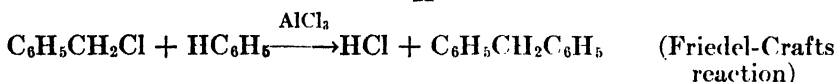
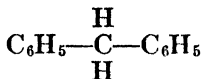
(3) Mesitylene, 1,3,5-trimethylbenzene, may be prepared from acetone by loss of water (see equation, page 158). Here, again, we have a method of passing from the aliphatic to the aromatic series of compounds.

#### ARYL DERIVATIVES OF ALIPHATIC COMPOUNDS

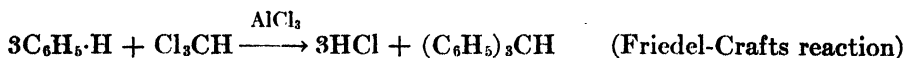
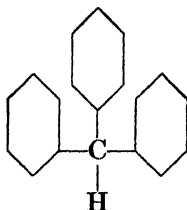
As toluene,  $C_6H_5\cdot CH_3$ , may be looked upon as benzene with methyl group substituted for hydrogen (an aliphatic or alkyl derivative of benzene), so it is equally correct to consider this compound as derived from methane by replacement of the phenyl group for hydrogen (an aromatic or *aryl* derivative of methane). The names methylbenzene and phenylmethane represent these two conceptions of toluene.

The question at once arises whether similar aromatic derivatives of ethylene and acetylene exist, and we find this to be the case. Also, derivatives of methane, ethane, etc., are known in which several aryl groups are substituted for hydrogen. None of these compounds can be studied in any detail in this book; however, the structures and methods of formation of several examples are added in order to illustrate the possibilities in these series.

##### Diphenylmethane :



##### Triphenylmethane :

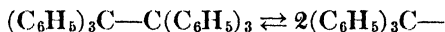


**Free Radicals.** Almost from the outset of the science of organic chemistry there has been an interest in the existence and isolation of those groups (methyl, ethyl, etc.) which we call radicals. It was conceived that compounds were formed by union of various groups with a certain radical, therefore it should in some way be possible to free and isolate the radical. When Bunsen made cacodyl he thought he had such a radical; similarly when butane was synthesized it was thought to be free ethyl.

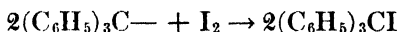
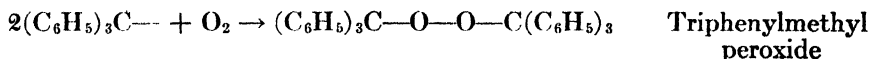
The first actual case in which a free radical was noted occurred in 1900, when Gomberg tried to make hexaphenylethane by the action of silver on triphenylchloromethane:



The solution was found to contain a highly reactive compound which could readily add oxygen or hydrogen or iodine. The solution was yellow in color, while if the above reaction had taken place it should have been colorless. Subsequent research has shown that hexaphenylethane actually exists, but that in solution in a non-polar solvent it is dissociated into free radicals:



The free radical reacts with great avidity with oxygen, etc.



The heavy loading of the carbon atoms of ethane with aromatic groups has a weakening effect on the bond between them.

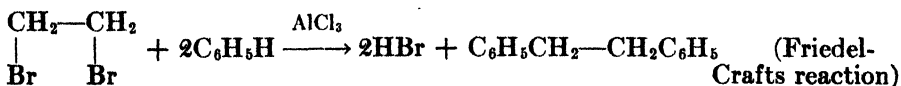
In solution, triphenylmethyl is in equilibrium with hexaphenylethane. The per cent of dissociation is 9.6% when one mole of hexaphenylethane is dissolved in 98 liters of benzene at 20°C. Further research in this interesting field has produced compounds containing trivalent carbon which are capable of isolation. Thus when tribiphenylmethyl chloride,  $((\text{C}_6\text{H}_5\cdot\text{C}_6\text{H}_4)_3\text{CCl})$ , is treated with an active metal, tribiphenylmethyl,  $((\text{C}_6\text{H}_5\cdot\text{C}_6\text{H}_4)_3\text{C})$ , is produced. This is a violet-colored compound in solution, and in the solid state is a gray-green powder, extremely reactive and unstable.

We are also familiar with nitrogen compounds, built up on the same plan as hexaphenylethane, which dissociate in a similar manner. An example is tetraphenylhydrazine:

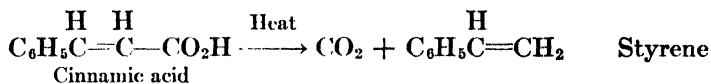


† Free radicals of the aliphatic series have been made by heating organo-metallic compounds. For example, tetramethyllead is heated in a tube through which a stream of hydrogen is passing. Lead and free methyl are produced. If a thin mirror of metal be deposited on the inner wall of the tube at a point just beyond the reaction zone, it will be removed by reaction with the methyl radical (formation of organometallic compound). The radical exists in the free state but a fraction of a second. Aliphatic free radicals have also been formed by the action of ultraviolet light upon aliphatic aldehydes and ketones (1936).

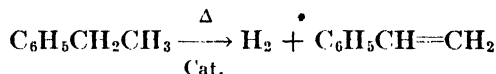
**Diphenylethane:**  $\text{C}_6\text{H}_5\text{CH}_2-\text{CH}_2\text{C}_6\text{H}_5$



**Phenylethylene, styrene, or vinylbenzene:**  $\text{C}_6\text{H}_5\overset{\text{H}}{\text{C}}=\text{CH}_2$

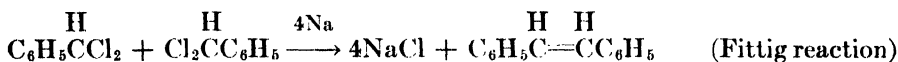


**Styrene is made commercially** by dehydrogenation of ethylbenzene; this in turn is made from ethylene and benzene through the Friedel-Crafts reaction (page 576).

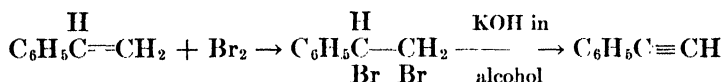


Styrene easily polymerizes to a thermoplastic resin of high dielectric constant and fine appearance. The use of styrene in the making of plastics and synthetic rubber is noted on pages 505 and 625.

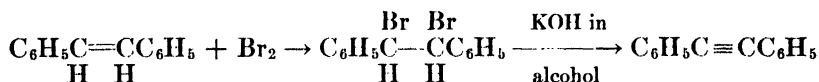
**Diphenylethylene (symmetrical), Stilbene:**  $\text{C}_6\text{H}_5\overset{\text{H}}{\text{C}}=\overset{\text{H}}{\text{C}}\text{C}_6\text{H}_5$



**Phenylacetylene:**  $\text{C}_6\text{H}_5\text{C}\equiv\text{CH}$



**Diphenylacetylene, Tolane:**  $\text{C}_6\text{H}_5\text{C}\equiv\text{CC}_6\text{H}_5$



## REACTIONS OF AROMATIC HYDROCARBONS

The aromatic hydrocarbons are not sharply differentiated from those of the aliphatic series by their physical properties, but their chemical behavior sets them entirely apart from the compounds we have studied. It will be well to review briefly the chemical unlikeness of these two groups, taking up the several items in greater detail in further paragraphs.

(1) *Oxidation.* The aliphatic saturated hydrocarbons resist oxidation as a rule, while aromatic hydrocarbons having side-chains are readily oxidized to aromatic acids.

(2) *Substitution.* Aromatic hydrocarbons undergo substitution with chlorine or bromine as do the paraffins. In addition, they react with nitric acid to form the highly important nitro compounds, and with sulfuric acid to produce the sulfonic acids, compounds of wide usefulness. These last two reactions are characteristic of the aromatic hydrocarbons, since neither nitric nor sulfuric acid successfully attacks the paraffins unless special con-

ditions are provided. Therefore, these reactions may be used to distinguish one class from the other (page 772).\*

With regard to the attack of halogens upon aromatic hydrocarbons, it may be said that more is known of this reaction than of the corresponding reaction with the paraffins. For example, while it would be difficult to state which hydrogens of hexane would in order be substituted by bromine, certain regularities in the behavior of the aromatic compounds would allow us to predict this succession in the case of benzene and certain other compounds of its series. We will now consider the reactions of benzene.

### REACTIONS OF BENZENE

(1) *Oxidation.* In the oxidation of benzene at 450°C., using air, with vanadium oxide as a catalyst, we obtain maleic anhydride. In general it is not feasible to obtain intermediate products from benzene oxidation. Either there is no effect or the oxidation goes out of bounds to yield carbon dioxide and water.

(2) *Reduction.* The complete reduction of benzene yields hexahydrobenzene, or cyclohexane. This reduction may be accomplished by passing benzene vapor, mixed with hydrogen, over finely divided nickel at an elevated temperature (Sabatier and Senderens reaction):

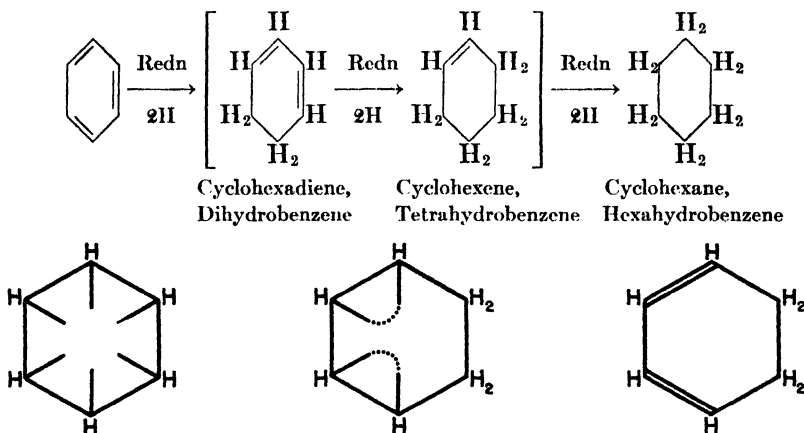


FIG. 76.—Benzene: not olefinic in character.

FIG. 77.—Partially reduced. Centric symmetry destroyed.

FIG. 78.—Dihydrobenzene, Cyclohexadiene. Olefinic in character.

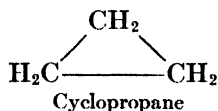
Cyclohexadiene and cyclohexene, which represent intermediate steps in the reduction of benzene, are not prepared by direct reduction, but by other methods. These two compounds resemble aliphatic olefins in their behavior, undergoing addition reactions impossible to benzene, and being much more

\* Those properties which confer "aromaticity" upon a ring compound include: (1) easy substitution of ring hydrogen, (2) resistance to oxidation and addition reactions, (3) acidity of hydroxyl-substituted compounds.



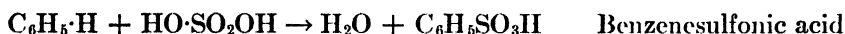
easily oxidized than is benzene. The Armstrong and Baeyer formula for benzene was proposed to show plainly that benzene itself has no double bonds until two valences of the centric cluster have been withdrawn, thus explaining why the reduction products dihydrobenzene and tetrahydrobenzene act like olefins, while benzene does not (see Figs. 76-78).

Cyclohexane or hexahydrobenzene is sometimes called hexamethylene, as the ring is formed of six methylene groups. It belongs to a series of compounds called the cycloalkanes or cycloparaffins which are known from cyclopropane to cyclotriacontane,  $C_{30}H_{60}$ . These compounds have the



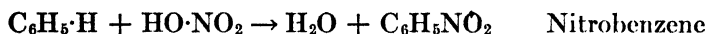
behavior of aliphatic hydrocarbons; they may be considered as forming a connecting link between the aliphatic and the aromatic series. They will be discussed in Chapter XXXII.

(3) *Reaction of benzene with sulfuric acid; sulfonation.*



The sulfonic acids are separately discussed in Chapter XXII.

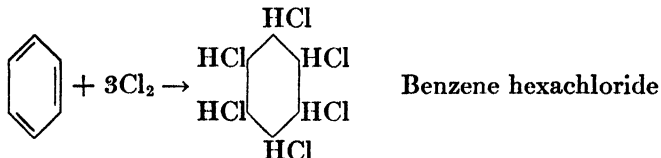
(4) *Reaction with nitric acid; nitration.*



See Chapter XXIII, for discussion of nitrobenzene.

For mercuration and arsonation of benzene, see Chapter XXXI.

(5) *Reactions with the halogens; halogenation.* In direct sunlight, benzene and chlorine react by addition to form benzene hexachloride:



In the presence of a carrier,\* benzene reacts with bromine to form monobromobenzene:



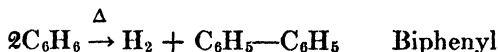
With rise of temperature and addition of bromine, a dibromobenzene results:



For action of iodine, see page 430.

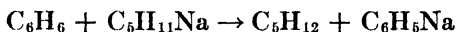
\* See footnote, page 86.

(6) *Effect of heat.* Pyrolysis of benzene causes loss of hydrogen with the consequent formation of polynuclear compounds:



Biphenyl is formed when benzene is passed through a hot iron pipe. Other hydrocarbons (*p*-diphenylbenzene, 1,3,5-triphenylbenzene, etc.) are formed in smaller yield.

(7) *Metalation of benzene.* When benzene is treated with an alkali alkyl an exchange occurs:



At the same time some disubstitution occurs. When the metalated benzene mixture is treated with carbon dioxide, benzoic acid is formed in good yield, together with small amounts of benzenedicarboxylic acids.

*Physiological Action.* Benzene is a highly toxic compound. Taken internally it causes death by paralysis of respiration. The vapor when inhaled may cause death if sufficiently concentrated. If breathed over a long period there are changes in the blood corpuscles which may be fatal. Contact with the skin is also harmful. Toluene is more toxic and the xylenes are less toxic than benzene.

*Deuterium Exchanges.* Hexadeuteriobenzene, benzene-*d*<sub>6</sub>, C<sub>6</sub>D<sub>6</sub>, has been made by shaking benzene with D<sub>2</sub>SO<sub>4</sub> for several days. The acid if over 90% strength will cause sulfonation. Benzene also exchanges some hydrogen for deuterium when shaken with D<sub>2</sub>O (platinum catalyst). It is reported that some substituted benzenes exchange their nuclear hydrogen for deuterium when treated with D<sub>2</sub>O or with acids even more readily than does benzene. The properties of C<sub>6</sub>D<sub>6</sub> are as follows: M.p., 6.8°C.; B.p., 79.3°C.; D<sub>25</sub><sup>°</sup>/25°, 0.9456; D<sub>25</sub><sup>°</sup>/4°, 0.9429.

TABLE 34.—COMPARISON OF PROPERTIES OF DEUTERIUM AND HYDROGEN, WATER AND HEAVY WATER

B.p.	Hydrogen, 20.38°K.	Deuterium, 23.5°K.
	Water	Heavy water
B.p.....	100.0°C.	101.42°C.
M.p.....	0.0	3.802
Density 25°/25°.....	1.0000	1.1079
Temp. max. density.....	4.0°	11.6°
Surface tension.....	72.75 dynes/cm.	67.8 dynes/cm.
Ionization constant.....	1.04 × 10 <sup>-14</sup>	0.33 × 10 <sup>-14</sup>

### REACTIONS OF BENZENE HOMOLOGS

These reactions are separately treated, as important differences are found between the reactions of compounds with and without side-chains.

## GENETIC RELATIONSHIPS OF BENZENE

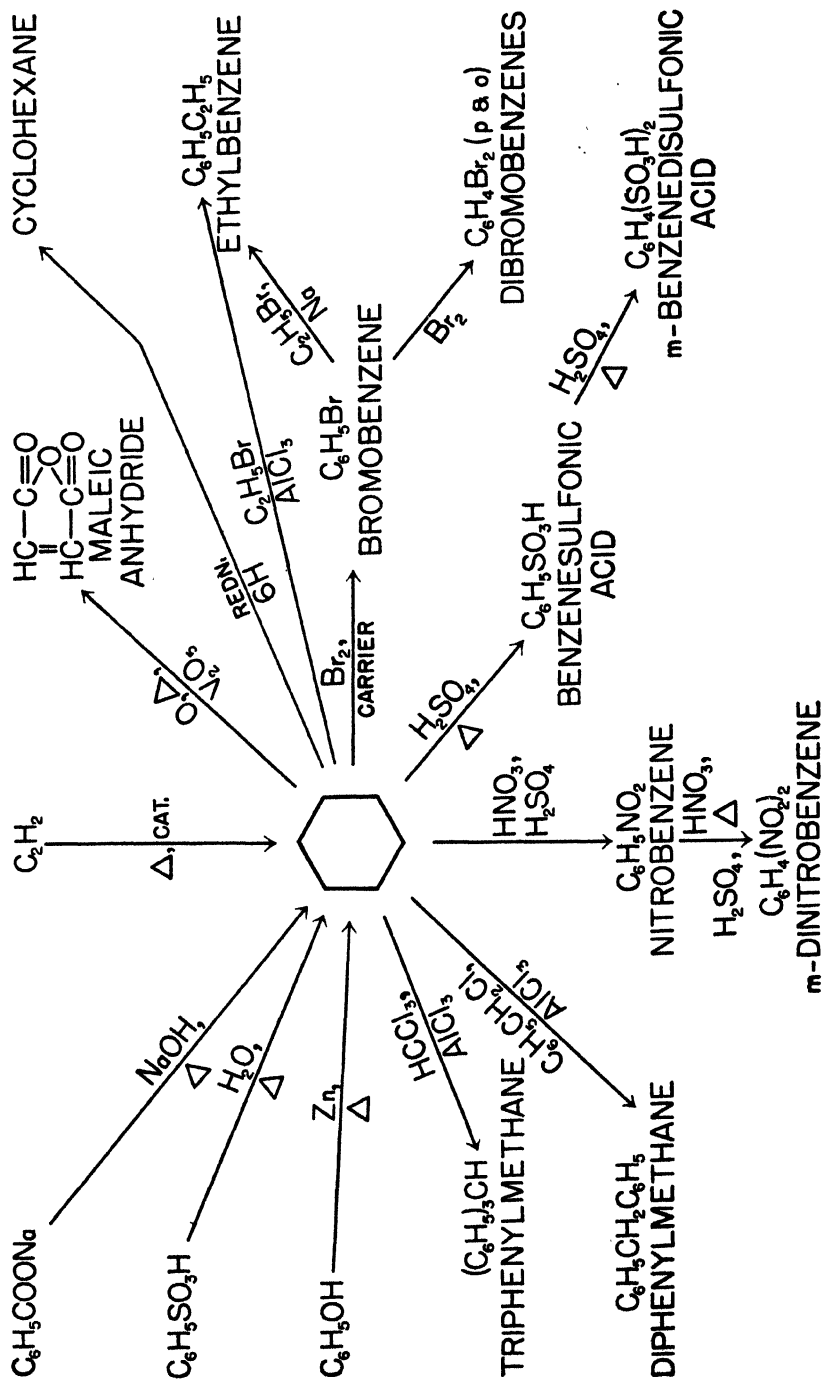
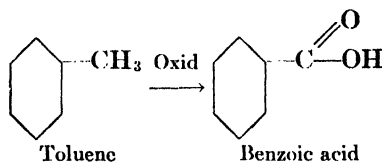


CHART VII.

(1) *Oxidation.* The oxidation of benzene yields various products according to the conditions. The complete oxidation of any alkyl side-chain always leads to the production of the carboxyl group:



Primary alcohol and aldehyde represent intermediate stages of this oxidation (see aliphatic acids). Thus toluene may be oxidized to benzoic acid as shown above, or it may be so treated as to yield benzyl alcohol,  $\text{C}_6\text{H}_5\text{CH}_2\text{OH}$ , or benzaldehyde,  $\text{C}_6\text{H}_5\text{CHO}$ . It is interesting to note that certain bacteria can promote oxidation of benzene, toluene, etc.

(2) *Reaction with halogens.* The action of benzene homologs towards the halogens is peculiar. It may be illustrated by the reactions with toluene. Chlorine reacts with boiling toluene to form a derivative in which hydrogen of the side-chain is substituted; the product is benzyl chloride,  $\text{C}_6\text{H}_5\text{CH}_2\text{Cl}$ .

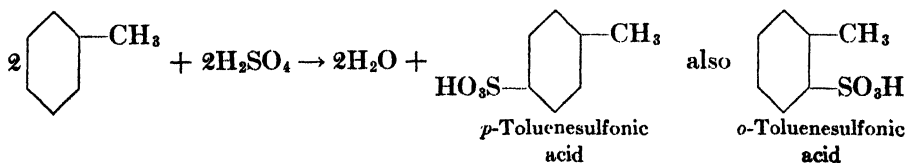
H

Additional chlorine reacts to form benzylidene chloride,  $\text{C}_6\text{H}_5\text{CCl}_2$ , and benzylidene chloride,  $\text{C}_6\text{H}_5\text{CCl}_3$ .

The same results are secured when the reaction between chlorine and toluene is carried out in direct sunlight.

The course of this reaction is entirely altered when a carrier is employed. In this event, chlorine atom substitutes for hydrogen of the benzene nucleus, forming *p*- and *o*-chlorotoluenes. With additional chlorine, and by use of a higher temperature, successive hydrogen atoms of the nucleus may be replaced, forming dichlorotoluene, etc. The above remarks show that the action of halogens upon a homolog of benzene is strongly influenced by the conditions of the experiment. The presence of a carrier causes substitution to take place in the ring, and vice versa.

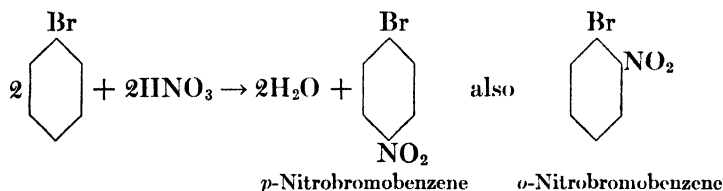
The nitration or sulfonation of benzene homologs is easily carried out. The action is one of substitution of hydrogen of the nucleus, and does not usually affect the side-chains (see footnote, page 444). Thus, sulfuric acid with toluene produces *p*-toluenesulfonic acid together with *o*-toluenesulfonic acid:



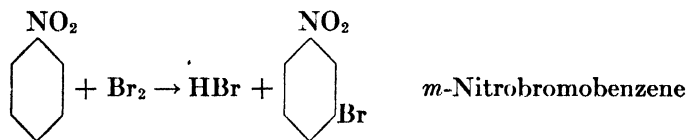
## ORDER OF SUBSTITUTION IN THE BENZENE NUCLEUS

When several hydrogen atoms in benzene are successively replaced by substituting groups, it is noted that the entering groups are not oriented about the ring in a haphazard or chance manner. On the contrary, the hydrogen atoms of the nucleus are replaced in a definite order. The position taken by an entering group depends primarily upon the nature of the group already on the ring, although temperature, concentration, etc., have a secondary effect. Very seldom do we secure equal amounts of *ortho*, *meta*, and *para* isomers; either there is a preponderance of the *para* and *ortho* isomers, or the *meta* isomer forms the chief product of reaction. The choice between these two types of reaction is usually independent of the nature of the group being introduced.

For example, the nitration of bromobenzene yields *p*- and *o*-nitrobromobenzenes:



while the bromination of nitrobenzene produces *m*-nitrobromobenzene:



In the first instance, the presence of bromine in the ring caused the entering nitro group to seek carbons 4 and 2; in the second case, the nitro group already present caused substitution of bromine to occur on carbon 3.

The regularities of substitution observed have received several classifications, one of which, the rule of Crum Brown-Gibson, is as follows:

**Crum Brown-Gibson Rule (1892).** If X be a group attached to a benzene ring, we have the following possibilities: (a) If HX can be directly oxidized, in one step, to HOX, *meta* derivatives will be obtained on further substitution; (b) If the above oxidation cannot occur, *para* and *ortho* substitution is the rule.\* Example: Consider nitrobenzene, C<sub>6</sub>H<sub>5</sub>NO<sub>2</sub>; X then

\* In many reactions of substitution, all three forms of the di-derivatives will be produced. These rules merely seek to denote which isomers form the chief product of reaction in any given case. Such factors as temperature, concentration, etc., will always have an influence on the course of substitution; the statements presented are therefore not to be construed as "laws of substitution."

stands for  $\text{NO}_2$  and  $\text{HX}$  for  $\text{HNO}_2$ . Now nitrous acid can be directly oxidized to nitric acid,  $\text{HONO}_2$ ; therefore, nitrobenzene will give *meta* derivatives on nitration, bromination, etc.

**Alternate presentation (Vorländer 1902).** The saturated side-chains give mainly *para* and *ortho* substitution products; however if the side-chain atom which abuts the ring has a double or triple bond, or is charged positively, *meta* substitution predominates.\* The *m*-directing effect diminishes as this key atom is removed from the ring along the side-chain.

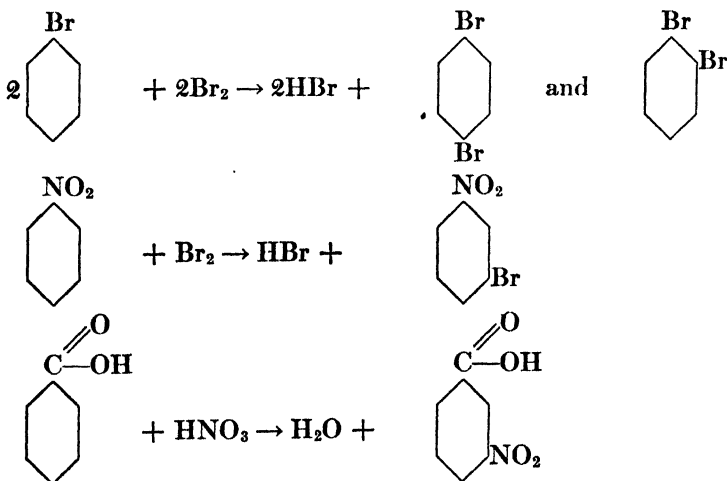
*Saturated side-chains*—give *para* and *ortho* derivatives. The relative amounts of *para* and *ortho* compounds secured depend upon temperature (high temperature favors *para* substitution in some instances, while in others it favors the *ortho* compound), concentration, nature of catalyst, nature of the group already on the ring, and of the group being introduced.

OH  
NH<sub>2</sub>  
Halogen  
Alkyl

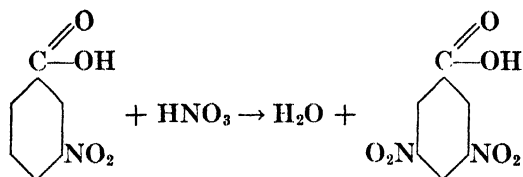
*Unsaturated side-chains*—give *meta* derivatives.

SO<sub>3</sub>H  
CO<sub>2</sub>H  
CHO  
NO<sub>2</sub>  
CN

Examples:



\* This presentation is not entirely correct. To date several exceptions have been found.



**Hammick-illingworth Rule.** If in the compound  $\text{C}_6\text{H}_5\text{XY}$ , Y is in a higher group of the periodic system than X (or if in the same group Y has lower atomic weight than X) a second group or atom will enter the *meta* position. All other cases, including those in which XY is a single atom, give *ortho-para* products.

Other sets of "rules" for orientation have been devised besides those given. It is recognized that the Crum Brown-Gibson rule is purely empirical as is that of Vorländer. The Hammick and Illingworth rule is practical and easily remembered. The more recent formulations have a basis of theory resting on the electronic structures of both benzene nucleus and entering group. There will not be space to discuss them here. For a recent empirical rule of considerable value see Reference 17, page 426.

**Analysis of a Mixture of o-m-p-Compounds.** One method of analysis of a solid mixture of *ortho*, *meta*, and *para* compounds is as follows: suppose that adding 1 g. of the pure *para* compound to 15 g. of the pure *meta* compound depresses the melting point of the *meta* compound  $3^\circ$ . Since the *ortho*, *meta*, and *para* compounds are isomers, we know that the same depression of melting point would occur if 1 g. of the *ortho* compound were mixed with 15 g. of the *meta* compound. Now let 1 g. of the unknown mixture be added to 15 g. of *meta* compound. Any effect on the melting point of the *meta* compound will be due only to the *ortho* and *para* compounds present in the mixture. Suppose the depression to be  $2^\circ$ . In this case the mixture contains approximately one-third *meta* compound. In a similar way the analysis may be extended to find the amounts of *ortho* and *para* compound present.

**Additional Facts.** The *para-ortho* orienting groups, excepting halogens, enhance the reactivity of the ring, i.e., benzene reacts more slowly with nitric acid than does phenol. While phenol nitrates easily with dilute nitric acid, benzene requires concentrated acid. *Meta*-directing groups retard the reactions of the ring. Thus the nitration of nitrobenzene requires more drastic conditions than the nitration of benzene.

The *para-ortho* directing groups have a greater directive power than the *meta*-directing groups. In case of a competition between a *para-ortho* directing and a *meta*-directing group we may expect the former to prevail. Among the *para-ortho* directing groups hydroxyl has the most powerful influence, the others following as indicated below:\*

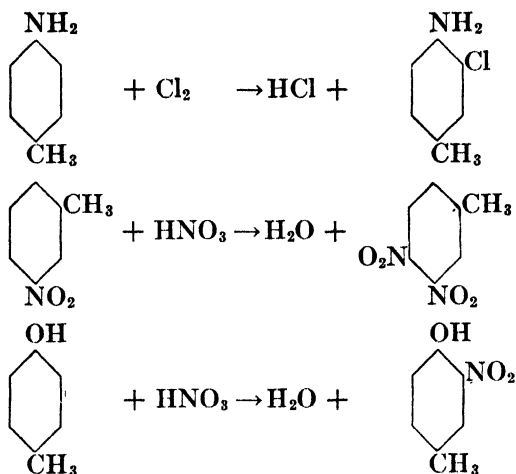


The  $\text{CO}_2\text{H}$  is most powerful of the *meta*-directing groups:



\* The order shown here is not infallible. Cases are known in which the order is different.

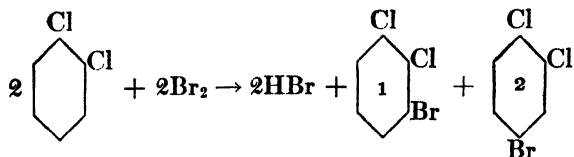
Examples:



#### DETERMINATION OF STRUCTURE OF BENZENE DI-DERIVATIVES. KÖRNER'S ABSOLUTE METHOD

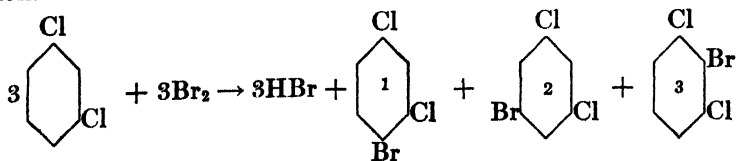
We have so far tacitly assumed the correctness of the structures presented for various substitution products of benzene; thus, bromination of nitrobenzene was said to produce *m*-bromonitrobenzene. It will now be necessary for us to consider the methods used by chemists to actually determine the structures of compounds produced in experiments like the above. Various methods exist, of which the most elegant is the "absolute" method of Körner. This method, assuming the correctness of the Kekulé formula for benzene, makes certain predictions based upon the formula as follows:

(1) An *ortho* di-derivative of benzene will yield two different tri-derivatives when an additional group is introduced.



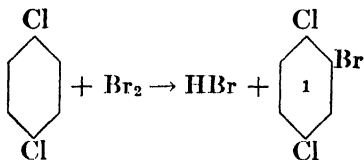
Thus, the bromination of *o*-dichlorobenzene can produce only two bromodichlorobenzenes.

(2) A *meta* di-derivative will yield three tri-derivatives on further substitution.



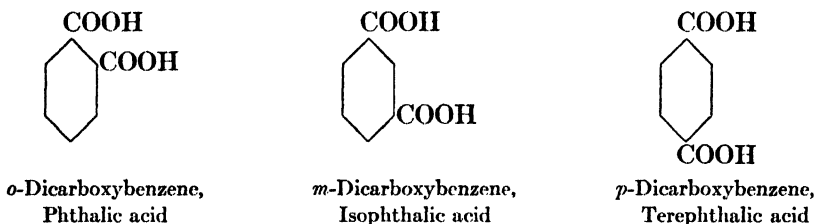


(3) A *para* compound will yield but one tri-derivative.\*



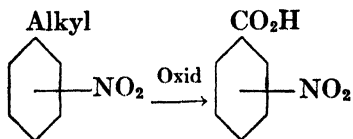
Hence, a di-derivative which on further substitution yields two different tri-derivatives, must have the *ortho* structure. One which gives three different tri-derivatives is *meta*, while a di-derivative which yields but one tri-derivative in this manner, is a *para* compound. Note that both side-chains of the original di-derivative *must be alike* or this rule does not hold (see page 403).

To assign the position of groups in the alkyl di-derivatives of benzene, use is made of the fact that all alkyl side-chains on complete oxidation revert to the carboxyl group (see page 413). Thus, any di-alkyl derivative of benzene upon oxidation must yield one of the following dicarboxylic acids:



These three acids have definite physical properties and are well known,† therefore the production of any one of them by oxidation of a dialkyl derivative of benzene at once fixes the structure of this compound.

There are other “key compounds,” similar to the phthalic acids, into which benzene derivatives may be converted by suitable reactions (as the dialkyl compounds are oxidized to phthalic acids). For example, if we have a nitro group and an alkyl group, we may by oxidation come to one of the known nitrobenzoic acids:



\* The student should satisfy himself by trial that the formulas above show all the possibilities which exist for the three types of di-derivatives.

† The chemical research by means of which the relative position of the groups in the phthalic acids has been determined is too difficult for inclusion in an elementary text.

Every time that the structure of a di- or polysubstituted derivative is learned, it may be used as a key compound for other derivatives, which can be transformed to the known compound by suitable reactions.

Today the structure of benzene derivatives may thus be learned by conversion of the unknown to one of the many compounds whose structure is already known as a result of past experimentation. Thus, the Körner method, which at the outset of research in aromatic chemistry was of the first importance, no longer holds this position.

## HOMOCYCLIC COMPOUNDS

Carbocyclic compounds have only carbon atoms in the nucleus or ring. They may be called homocyclic carbon compounds. When other elements take part with carbon in ring formation, the resulting compounds are called heterocyclic. Examples of the latter will be found in Chapter XXXIV. Below are shown the formulas and methods of synthesis of several aromatic hydrocarbons having more than one ring. Those of the type of naphthalene and anthracene are called "condensed," as their several rings are joined by more than one carbon atom.

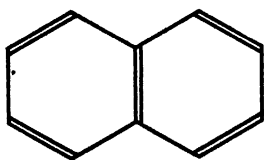


Fig. 79.—Naphthalene.

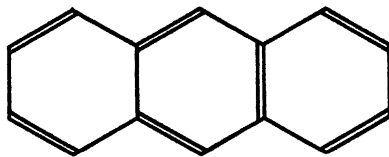
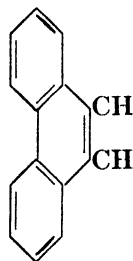
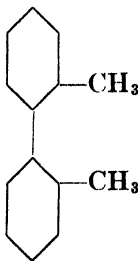


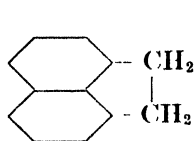
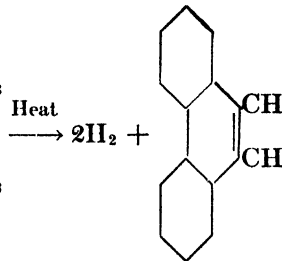
Fig. 80.—Anthracene.



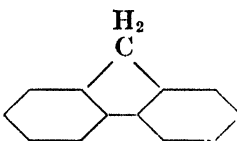
Phenanthrene



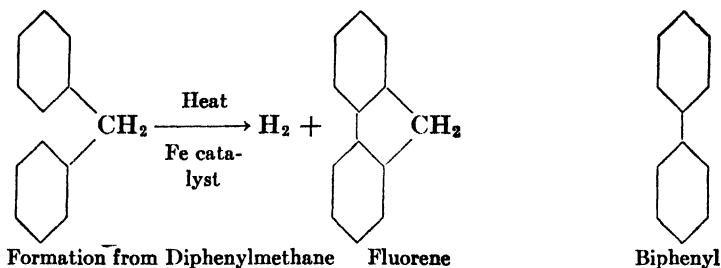
Formation from o-Ditolyl



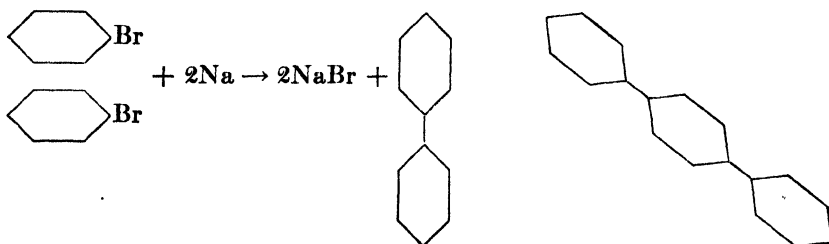
Acenaphthene



Fluorene



Biphenyl is made on a large scale by passing benzene vapor over a heated catalyst. Its formation is attended by loss of H-atom by each of two benzene molecules. Biphenyl is recommended as a boiler liquid for high-temperature boilers. Its high boiling point permits the use of high temperature at relatively low pressure. Various derivatives of biphenyl are being investigated since bulk production has reduced the price of this chemical. Continuous halogenation of biphenyl gives complex resinous compounds (Aroclor).

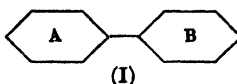


Formation of biphenyl from phenyl bromide by Fittig reaction.

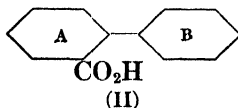
Terphenyl.  
Compounds of this type up to hexaphenyl are known.

Each of the above compounds (and also the other carbocyclic compounds not shown here, of which there are numerous examples) has some resemblance to benzene in its reactions, also many points of difference. Certain of these compounds will be mentioned in later developments of our subject. However, our attention will center principally upon benzene, and for a systematic knowledge of the reactions of these more complex hydrocarbons, the student should refer to the larger textbooks of organic chemistry.

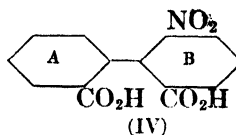
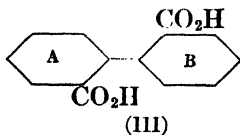
**Isomerism of Biphenyl Derivatives.** Interesting cases of stereoisomerism have come to light in a study of derivatives of biphenyl. We recognize this compound as belonging to the class discussed on page 328 in which a single bond exists between carbon atoms. It is quite evident that ring (A) below can rotate freely with reference to ring (B) about the bond which is common to both rings.



If we put a group on (A) *ortho* to the common bond, free rotation is still possible:



In (III) with a group on each ring in *ortho* position we still have free rotation:



If now a third group be placed in *ortho* position, free rotation is restricted (IV). The proof lies in the fact that compound (IV) can be separated into optically active forms. It is generally supposed that such compounds have the planes of the two rings at right angles to each other. The rings are coaxial but not coplanar. When free rotation is restricted, two molecular mirror-image forms are possible as shown here:

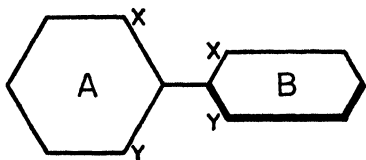


FIG. 81.

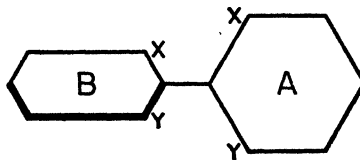


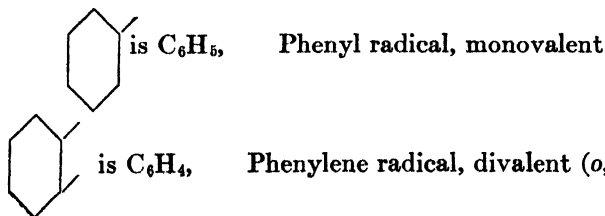
FIG. 82.

FIGS. 81, 82.—Mirror-image forms of biphenyl derivative. (A) in plane of paper. Plane of (B) at right angle to plane of paper.

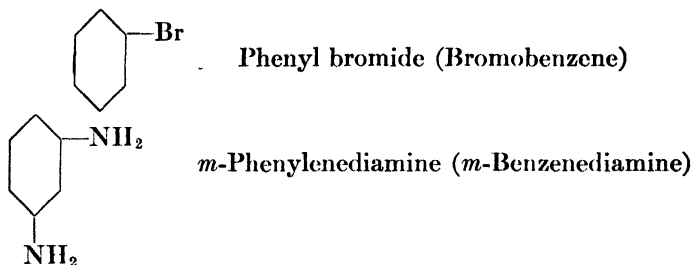
The restriction of free rotation depends primarily upon the size of the groups X and Y. If there is not room for them to "clear" each other, free rotation is prevented. The situation is then much the same as in the ethylene compounds discussed on page 59. The optical asymmetry of these biphenyl compounds depends on molecular asymmetry, there being no asymmetric carbon atoms present.

### RADICALS AND NOMENCLATURE

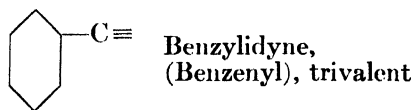
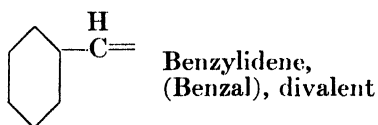
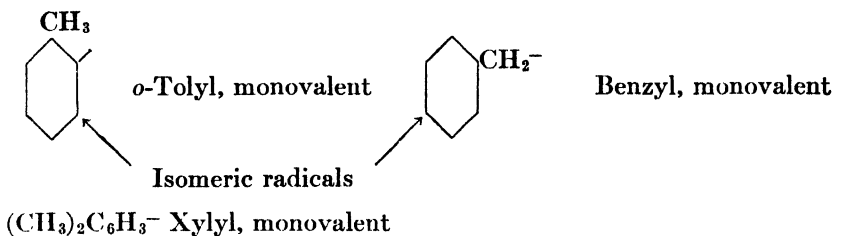
The names of the aromatic radicals (aryl radicals) are formed by use of the ending "yl" as in the aliphatic series. A few of the more common radicals are listed below. The symbol Ar is used for aryl radicals.



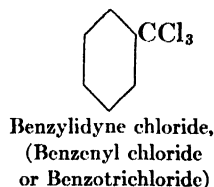
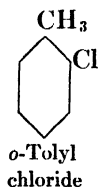
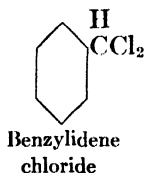
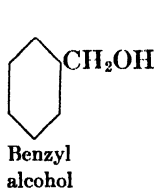
Examples showing nomenclature:



Radicals of benzene homologs:



Examples of nomenclature:



#### ALIPHATIC VERSUS AROMATIC COMPOUNDS

Several instances have been presented in these pages of the conversion of aliphatic type compounds to those of aromatic type, also numerous cases of the reverse type of reaction are known. It would, therefore, be perfectly proper to consider the aromatic compounds as derivatives of methane, as are those of the aliphatic group. The separation of these two groups is carried out in this book as a matter of convenience to expedite the student's progress.

Aromatic and aliphatic groups are alike in their possession of sub-groups or series, such as alcohols, aldehydes, acids, amines, etc. On the other hand,

these compounds frequently show striking differences in their reactions, according to their predominantly aliphatic or aromatic nature.

Aromatic compounds in general have higher molecular weights than aliphatic, thus many of the common examples are solids, which may be purified by crystallization. Although the reaction of substitution usually occurs more easily with aromatic than with aliphatic compounds, the latter more readily yield simpler substances on chemical treatment, as they lack the stable nucleus which characterizes the aromatic compounds. The behavior of the two groups toward oxidizing agents and especially toward nitric and sulfuric acids sets them apart.

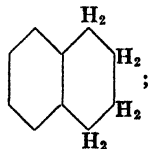
Any discussion of the relative importance of these two groups of compounds would be beside the mark, since both series are employed without favor by the chemist. We may note that the components of living cells, (fats, carbohydrates, proteins) embrace mainly aliphatic representatives, while a great many of the curative drugs and antiseptics are aromatic in character. The dyes also are chiefly aromatic derivatives.

Much more study has been expended upon aromatic compounds than is the case with the aliphatic, and as a consequence, more representatives of the former series are known. At the present time, emphasis is being placed upon the advantages of intensive research with aliphatic compounds. It is hoped that such study will yield a number of discoveries rivalling in importance those which have been made in the field of aromatic chemistry.

### REVIEW QUESTIONS

1. Give a résumé of the points for and against the Kekulé formula for benzene.
2. Write the graphic formulas for *o*-dibromobenzene, for 1,3-dinitrobenzene, for *p*-dichlorobenzene, for 3-chlorotoluene.
3. Write graphic formulas for: (a) *m*-Xylene; (b) Mesitylene; (c) Isopropylbenzene; (d) Tetraphenylmethane; (e) Styrene; (f) Tolane; (g) Stilbene; (h) Phenanthrene; (i) Anthracene.

4. Assign names to the following formulas. (a)  $C_6H_5CH_2CH_2CH_3$ ; (b)



- (c)  $C_6H_5CH_2CN$ ; (d)  $C_6H_5CH_2C_6H_4Cl$  (*p*)

5. Write equations for three methods for preparing benzene.
6. Show by equations two methods (each) for the preparation of: (a) Toluene; (b) Propylbenzene.
7. Summarize by equations the reactions of benzene.
8. Which of the reactions given in 7 are typical of the aromatic hydrocarbons?
9. Show by equations the reactions of chlorine upon toluene under various conditions.
10. What would be formed upon the oxidation of ethylbenzene?
11. How may the following replacements be made on the benzene ring? (a)  $-H$  by  $-Cl$ ; (b)  $-Br$  by  $-C_2H_5$ ; (c)  $-C_2H_5$  by  $-COOH$ ; (d)  $-H$  by  $-NO_2$ ; (e)  $-COOH$  by  $-H$ .
12. Write equations for the action of nitric acid upon toluene.
13. What compounds would result from the action of:

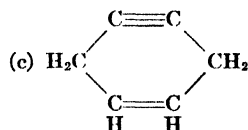
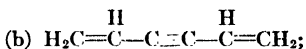
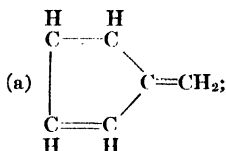
- (a) Nitric acid upon nitrobenzene?  
 (b) Sulfuric acid upon bromobenzene?  
 (c) Bromine upon benzenesulfonic acid?
14. How do homocyclic and heterocyclic compounds differ structurally from each other? Write the structures of compounds representative of each class.
15. Write the graphic formula for: (a) Benzenyl bromide; (b) Benzyl cyanide; (c) *m*-Tolyl bromide; (d) Phenylamine.
16. An aromatic hydrocarbon of formula  $C_8H_{10}$  yields upon oxidation a substance of formula  $C_7H_6O_2$ . What was the original compound?
17. An aromatic hydrocarbon of formula  $C_{10}H_{14}$  gave when oxidized an acid of formula  $C_8H_6O_4$ . Write a possible structural formula of the original compound and of its oxidation product.
18. Write equations showing the methods used to bring about the following changes: (a) Hydroxybenzene to benzene; (b) Benzoic acid to benzene; (c) Bromobenzene to ethylbenzene; (d) Toluenesulfonic acid to toluene; (e) Benzene to benzoic acid.
19. What products should be formed in largest yield by the following reactions:  
 (a) Action of iodine on *o*-toluidine?  
 (b) Action of nitric acid on *o*-nitrophenol?  
 (c) Action of nitric acid on *m*-dinitrobenzene?  
 (d) Action of nitric acid on *o*-nitrotoluene?  
 (e) Action of chlorine on *o*-nitrobenzoic acid?
20. The following prices are quoted from the catalog of a well known supply house:

<i>o</i> -Dichlorobenzene.....	100 g.	\$ 4.50
<i>p</i> -Dichlorobenzene.....	5000 g.	3.50
<i>m</i> -Dichlorobenzene.....	100 g.	9.00
<i>o</i> -Dinitrobenzene.....	100 g.	5.50
<i>m</i> -Dinitrobenzene.....	500 g.	4.50
<i>p</i> -Dinitrobenzene.....	10 g.	4.50
2,4-Dinitrobenzoic acid.....	100 g.	28.00
3,5-Dinitrobenzoic acid.....	500 g.	9.00

Explain the large differences between the prices asked for these isomeric compounds.

21. Sulfuric acid reacts with acetone to give a trimethylbenzene. What use can we make of this compound in assigning definite structures to the three possible trimethylbenzenes?
22. How make the following from toluene: (a) *m*-Nitrobenzoic acid; (b) *o*-Nitrobenzoic acid; (c) *m*-Bromobenzoic acid; (d) *p*-Bromobenzoic acid; (e) *o*-Chlorobenzylidene chloride?
23. Discuss the oxidation of ethylbenzene and of 2-ethyloctane.
24. How much potassium permanganate would be needed for the oxidation of one mole of toluene? The main products are benzoic acid,  $MnO_2$ , and KOH.
25. Write a series of equations showing how to make *m*-ethylbenzoic acid from benzene.
26. A benzene derivative has two side-chains in *meta* position. This is treated with bromine in such a way as to introduce one atom of bromine to the ring. Three new compounds and only three are formed. One of the side-chains of the original compound was  $CH_3$ . What was the other?
27. The distance between carbons of the benzene ring is 1.39 Å. What has this fact to do with the existence of isomers like those described on page 396?
28. How is nitric acid used to distinguish benzene from *n*-heptane?
29. Discuss the reaction of 2-heptene and of benzene with bromine-water.
30. Benzene burns with a very smoky yellow flame. What conclusion can one draw from this experiment? How does one proceed to test the conclusion further?
31. How do you account for the fact that two forms of stilbene are known?
32. What relationship exists between the coal tar industry and the steel industry?

33. Write formulas for the different isomeric chlorobromonitrobenzenes.
34. What facts make it possible to use the Fittig reaction for the production of ethylbenzene in fair yield from phenyl bromide, ethyl bromide, and sodium?
35. Write the formula for a monosubstitution product of styrene which could display geometrical isomerism.
36. Why was the Körner orientation method important in the early development of aromatic chemistry? Why has it lost its early importance?
37. An aromatic compound  $C_8H_{10}$  forms but one mononitro compound upon nitration. Write the formulas of both hydrocarbon and nitro compound.
38. The heat of combustion of benzene is 782 Calories. What has this fact to do with the Kekulé formula for benzene?
39. On page 394 the statement is made that the equivalence of all hydrogen atoms of benzene is shown by the fact that but one monosubstitution product of any kind can be made. What other and quite different conclusion might be drawn from the fact cited? Has this conclusion been tested? What was the result?
40. Cite those facts learned in the study of benzene which make it impossible to adopt any of the following proposed structures for benzene.



41. There are six possible isomeric diaminobenzoic acids (formula  $(NH_2)_2C_6H_3COOH$ ). Removal of the carboxyl group (decarboxylation) from these acids yields different diaminobenzenes as follows: Acid #1 (m.p.,  $191^\circ$ ) and Acid #2 (m.p.,  $210^\circ$ ) each yield a diaminobenzene (phenylenediamine) of m.p.,  $103^\circ C$ . Acids #3 (m.p.,  $140^\circ$ ), #4 (m.p.,  $228^\circ$ ), and #5 yield a phenylenediamine of m.p.,  $62^\circ$ . Acid #6 (m.p.,  $200^\circ$ ) gives a phenylenediamine melting at  $140^\circ C$ . Discuss these results and work out the structures of the six original acids and of the three phenylenediamines obtained from them.
42. The compound (A) contains 92.2% C and 7.7% H, and has a molecular weight of 104. Upon oxidation it yields an acid (B) which contains 68.7% C and 4.9% H. (A) adds chlorine to give (C) which contains 40.58% Cl. Work out the structure of (A).
- (R)43. \* The compound (A) contains 68.33% C, 6.40% H, and 25.27% Cl. Upon reaction with sodium hydroxide solution it yields the compound (B) which contains 78.7% C, 8.2% H, and 13.11% O. The oxidation of (A) produces an acid (C) containing 68.84% C, 4.92% H, and 26.23% O. Give possible structures for the compound (A) and its isomers. Show what compound would be formed from each of these upon oxidation and upon treatment with NaOH solution.

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\* See footnote, page 119.



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## HALOGEN DERIVATIVES OF AROMATIC HYDROCARBONS

We have seen (Chapter XX) that benzene may react with chlorine or bromine by addition, forming thereby benzene hexachloride or hexabromide. These compounds are not stable, but revert to trichloro- or tribromobenzene, respectively. The typical reaction between benzene and the halogens is that of substitution, in which hydrogen of the nucleus is displaced by halogen atom. The *aryl halides* are products of this reaction. Phenyl chloride,  $\text{C}_6\text{H}_5\text{Cl}$ , phenyl bromide,  $\text{C}_6\text{H}_5\text{Br}$ , dibromobenzene, and chlorotoluene are examples of such compounds.

In the case of toluene and other benzene homologs it has been shown that halogen may be substituted either in the nucleus or in the side-chain. Thus from toluene we may prepare the chlorotoluenes, benzyl chloride, or benzylidene chloride, etc. These two classes of derivatives are distinct in their properties and chemical reactions. The former type illustrates a true aryl halide, while the latter is actually aliphatic in character (as far as the halogen atom and side-chain are concerned). Such substances as benzyl chloride are included with aryl halides rather than with aliphatic halogen compounds because of their derivation from aromatic originals, and because the presence of the benzene nucleus allows them to participate in certain reactions characteristic of aromatic compounds in general.

## PHYSICAL PROPERTIES

The true aryl halides (halogen in the nucleus) are substances with distinct but not unpleasant odors. The monosubstitution products are liquids, while derivatives more highly substituted are solids. As a class they are insoluble in water and in concentrated sulfuric acid, but soluble in alcohol, ether, and other organic solvents. Many of these substances are volatile in steam. The effect of the halogen atom introduced in the benzene nucleus upon the boiling point and specific gravity of the resulting aryl halide increases markedly in the series F-Cl-Br-I. See Table 35, page 428.

Those compounds in which halogen atom has been substituted in the side-chain generally possess powerful odors and are lacrymatory (cause flow of tears).\* The following list shows the melting points, boiling points, and specific gravities of several representative derivatives of benzene and toluene.

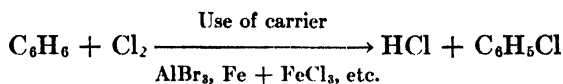
\* Several substances of this type were employed as poison gases in World War I, among them benzyl bromide, and xylyl bromide,  $\text{CH}_3\cdot\text{C}_6\text{H}_4\cdot\text{CH}_2\text{Br}$ . Aliphatic halogen compounds used as war gases are given on page 323, and additional aromatic compounds on page 606.

TABLE 35.—PHYSICAL CONSTANTS OF AROMATIC HALOGEN COMPOUNDS

Name	Formula	M.p., °C.	B.p., °C.	Sp. g., 20°/4°
Fluorobenzene	C <sub>6</sub> H <sub>5</sub> F	-41.2	85-6	1.024
Chlorobenzene	C <sub>6</sub> H <sub>5</sub> Cl	-45.2	132.1	1.107
Bromobenzene	C <sub>6</sub> H <sub>5</sub> Br	-30.6	156.2	1.495
Iodobenzene	C <sub>6</sub> H <sub>5</sub> I	-28.5	188.6	1.824 <sup>25°</sup>
Dichlorobenzene ( <i>o</i> )	C <sub>6</sub> H <sub>4</sub> Cl <sub>2</sub>	-17.6	179	1.305
Dichlorobenzene ( <i>m</i> )		-24.8	172	1.288
Dichlorobenzene ( <i>p</i> )		53	174	1.458
Dibromobenzene ( <i>o</i> )	C <sub>6</sub> H <sub>4</sub> Br <sub>2</sub>	1.8	221-2	1.956
Dibromobenzene ( <i>m</i> )		-6.9	219	1.952
Dibromobenzene ( <i>p</i> )		87-8	218.6	2.261
Diiodobenzene ( <i>o</i> )	C <sub>6</sub> H <sub>4</sub> I <sub>2</sub>	27	286.5	
Diiodobenzene ( <i>m</i> )		40.4	284.7	
Diiodobenzene ( <i>p</i> )		129.4	285	
Benzyl chloride	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> Cl	-39	179.4	1.120°/20°
Benzyl bromide	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> Br	-4	198-9	1.443 <sup>17°</sup>
Benzyl iodide	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> I	24.1	93 <sup>10</sup>	1.734 <sup>25°</sup>
Benzylidene chloride	C <sub>6</sub> H <sub>5</sub> CHCl <sub>2</sub>	-16.1	214	1.295 <sup>16°</sup>
Benzylidene bromide	C <sub>6</sub> H <sub>5</sub> CHBr <sub>2</sub>		140 <sup>20</sup>	1.51 <sup>16°</sup>
Benzylidene chloride	C <sub>6</sub> H <sub>5</sub> CCl <sub>3</sub>	-21.2	220.7	1.381 <sup>4°</sup>
Chlorotoluene ( <i>o</i> )	ClC <sub>6</sub> H <sub>4</sub> CH <sub>3</sub>	-34	159.5	1.082
Chlorotoluene ( <i>m</i> )		-47.8	161.6	1.072
Chlorotoluene ( <i>p</i> )		7.5	162.2	1.07
Bromotoluene ( <i>o</i> )	BrC <sub>6</sub> H <sub>4</sub> CH <sub>3</sub>	-28	181.8	1.422
Bromotoluene ( <i>m</i> )		-39.8	183.7	1.41
Bromotoluene ( <i>p</i> )		28.5	184-5	1.39
Iodotoluene ( <i>o</i> )	IC <sub>6</sub> H <sub>4</sub> CH <sub>3</sub>		211-2	1.698
Iodotoluene ( <i>m</i> )			204	1.698
Iodotoluene ( <i>p</i> )		35-6	211.5	

## PREPARATION

(1) The nuclear monohalogen compounds (true aryl halides) may be prepared by direct action of a halogen upon benzene:



The chlorination of benzene is carried out in the presence of iron or iron and ferric chloride.\* Cooling is necessary to keep the temperature at about 40°, and somewhat less than the calculated amount of chlorine is used to avoid the production of dichlorobenzenes. The crude product is freed from hydrogen chloride, and purified by distillation.

Free halogen (Cl<sub>2</sub>, Br<sub>2</sub>) may be used for halogenation, but it is also feasible and desirable in some instances to use derivatives. Examples of

\* See footnote, page 86, referring to the action of halogen carriers.

PAUL SABATIER. (French, 1854-1941.) Sabatier's early work was in the field of physical chemistry. He later turned to the organic field. He is best known for pioneering work in hydrogenation. He received the Nobel prize in 1912. See *J. Chem. Education*, 7, 1488 (1930); also this book, page 409.

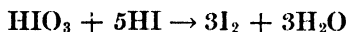


ARTHUR HANTZSCH. (1857-1935, German.) Known for his theory (with Werner) regarding the stereochemistry of nitrogen, for much valuable synthetic work, and for his theory of chromoisomerism (change of color of dyes and indicators associated with structural change). See *J. Chem. Soc. (London)*, 1936, 1051; also this book, page 481.

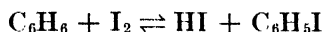
*Journal of the Chemical Society (London).*

such are sulfuryl chloride (used for nuclear substitution with the chlorides of iron, aluminum, antimony; used for side-chain substitution with chlorides of phosphorus, arsenic, bromine), sodium hypochlorite, organic peroxides.

Substitution takes place more readily than with aliphatic hydrocarbons,\* especially when a carrier is employed. With increase of temperature and additional halogen, the di-halogen derivatives, etc., are formed. Iodine derivatives cannot be formed in this manner, except at high temperature and under conditions which remove the hydrogen iodide as it is formed. This latter may be accomplished by the use of iodic acid:



Nitric acid may also be used to oxidize the hydrogen iodide. If hydrogen iodide is not removed, the reaction in this case is reversible:



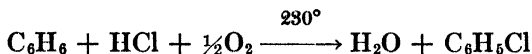
In preparing fluorine compounds indirect means are used, as direct fluorination is ordinarily a very violent reaction.

(2) The action of phosphorus trihalide or pentahalide on a phenol gives a small yield of aryl halide. The phosphorus pentahalide is preferred for this reaction.

With aromatic compounds this is in general not a practical method by which to form the halogen derivatives, while in the aliphatic series the production of halogen compounds by treatment of alcohols with phosphorus halide can be effected in many cases.

(3) A very important indirect method for the preparation of aryl halides, especially useful for the iodo and fluoro compounds, is found in the decomposition of certain diazonium salts (Sandmeyer reaction). The steps involved in this synthesis are shown on page 483. The Sandmeyer reaction is also useful in cases in which direct halogenation would not give the desired placement of halogen atom.

(4) A recent method for the preparation of chlorobenzene involves heating a mixture of benzene and hydrogen chloride with air in presence of a catalyst:



This method is important in connection with the preparation of phenol.

**Polyhalogenation.** By raising the temperature of halogenation and employing a higher percentage of reagent, the dihalogen derivatives of benzene are formed. Only a few per cent of the *meta* compound results, most of the yield consisting of *para* and *ortho* compounds. The ratio of *para* to *ortho* compounds in the preparation of the dibromobenzenes (iron

\* Certain groups facilitate the bromination and chlorination of benzene, notably OH and NH<sub>2</sub>. Phenol, C<sub>6</sub>H<sub>5</sub>OH, and aniline, C<sub>6</sub>H<sub>5</sub>NH<sub>2</sub>, may be brominated by the use of bromine-water.

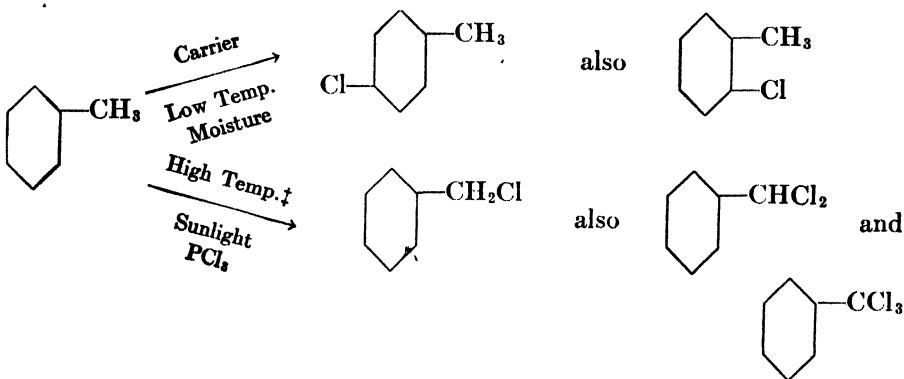
catalyst) is about 7:1. This *para-ortho* ratio varies in different halogenations according to the temperature and catalyst employed. Upon cooling such a mixture the *para* compound often separates as a solid which is easily purified. The *ortho* isomer contains dissolved *para* compound, and since the *ortho* and *para* compounds have almost identical boiling points (see table) a distillation is not practical. For the reasons given here indirect methods are often used to make the *meta* and *ortho* compounds. These methods will be given in later chapters.

Continued chlorination of benzene gives trichlorobenzenes (mainly the 1,2,4-compound) and tetrachlorobenzenes, finally hexachlorobenzene.

The halogens retard nuclear reactions of benzene though they belong to the *para-ortho* directing group (see page 416).

### PREPARATION OF HALOGEN DERIVATIVES OF BENZENE HOMOLOGS

(1) As already explained (page 413) the position taken by halogen atom (in nucleus or side-chain) is determined by the presence or absence of a carrier,\* the temperature employed, and the use or absence of sunlight or ultraviolet light. The conditions involved are briefly indicated in the following scheme representing the reaction of toluene and chlorine (for convenience the reagent and by-product are omitted):†



In laboratory chlorinations it is convenient to introduce chlorine until the gain in weight corresponds to that calculated for the reaction. In large-scale work the change in specific gravity may be used as an index of the progress of the reaction.

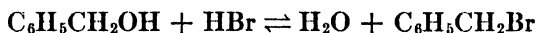
\* This is the most important variable.

† These rules of substitution must not be too rigidly applied; like the Brown-Gibson rules they show what will be the *chief product* in a given case. The halogenation of a hydrocarbon at the boiling point will affect the nucleus to some extent, while halogenation in presence of a carrier will produce a certain amount of side-chain substitution.

‡ The presence or absence of moisture also is important. Recent work has shown that peroxides greatly increase the rate of bromination and chlorination of toluene, apparently favoring side-chain substitution.

By successive alternate treatments halogen may be placed both in nucleus and side-chain, as found in *p*-chlorobenzyl chloride.

(2) Methods used to form alkyl halides are applicable for the introduction of halogen into the side-chains of aromatic compounds. Thus benzyl alcohol with hydrogen bromide yields benzyl bromide:



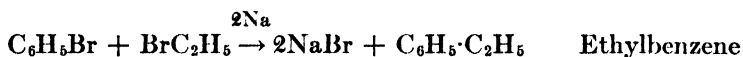
To repeat—introduction of halogen into aliphatic side-chains of aromatic compounds may be effected by methods successful in the aliphatic series, while halogen is usually placed in the benzene nucleus by direct halogenation, or by the use of the Sandmeyer reaction.

### REACTIONS

The reactions of the true aryl halides and the side-chain halogen compounds are illustrated in the examples given below. While the substances last mentioned claim all of the reactions of alkyl halides, the true aryl halides are far less reactive. The halogen atoms of such compounds are easily removed only by an active metal, as in the Fittig and Grignard reactions. The aryl halides therefore do not fill the same position as synthetic agents as do those of the aliphatic series. Special, and perhaps expensive, means are needed to enhance their reactivity.

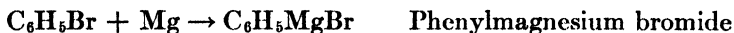
(1) Halogen in the nucleus (tightly held).

(a) *Wurtz-Fittig reaction*:



The mechanism of this reaction has been given (page 405).

(b) *Formation of Grignard reagent*:



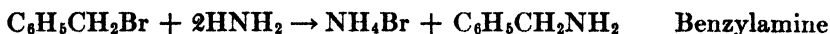
(2) Halogen in side-chain (loosely held). The reactions are like those of aliphatic halides (see Chapter IV for review).

The halogen when next the ring, as in benzyl bromide, is more easily removed than in the corresponding alkyl halide.

(a) *Hydrolysis*:



(b) *Amine formation*.



(c) *Formation of Grignard reagent*:

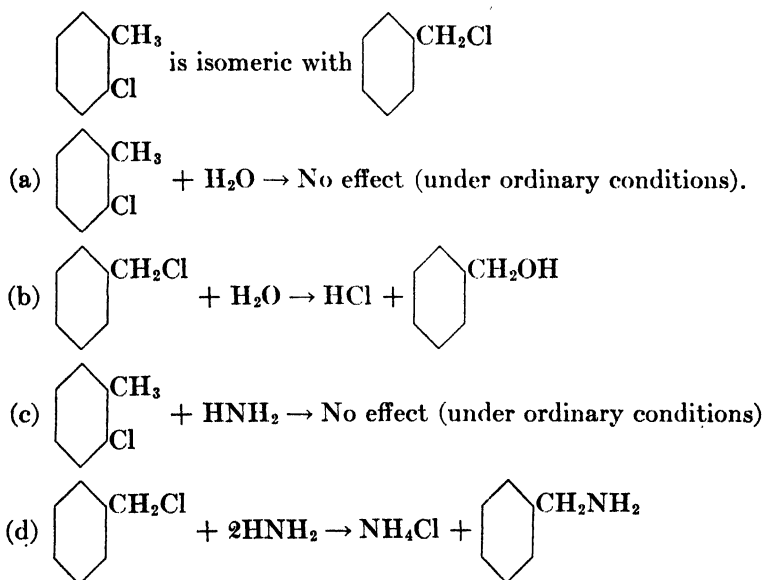


(d) *Oxidation:*


The difference in character between the true aryl halides and those derivatives in which halogen is found in the side-chain should again be emphasized. The former are not subject to hydrolysis under ordinary conditions\* and they do not react by double decomposition with anything like the same facility as do the side-chain halides (aralkyl halides).†

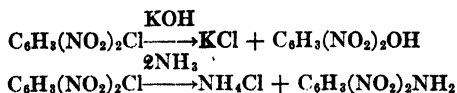
Isomers belonging to the two classes may easily be distinguished by reason of the above differences.

Example:



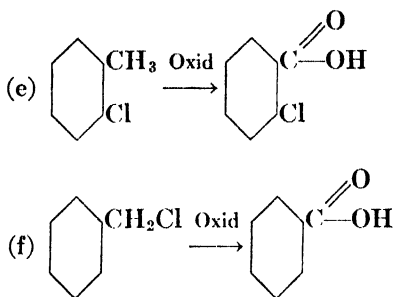
\* By using high temperature and pressure and a catalyst, the replacement of chlorine of the ring by hydroxyl or amino group may be brought about. The application of this method is relatively recent, but large amounts of phenol and aniline are now being made in this way. (See pages 459, 495.)

† The attachment of halogen to the carbon of the benzene nucleus is loosened by the substitution of nitro groups, especially when these are *ortho* to the halogen atom. Thus in dinitrochlorobenzene, (1,3,4) the chlorine atom behaves like that of an alkyl halide and is readily replaced.



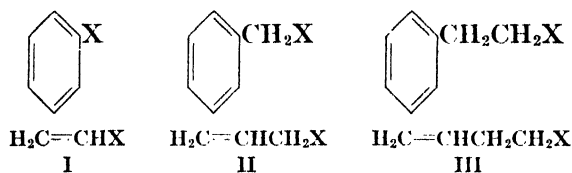
*p*- and *o*-Nitrochlorobenzenes react in a similar way and are used to make the corresponding nitrophenols and nitroanilines.





**Structure of Compounds.** We noted on page 88 that vinyl bromide, in which the halogen atom is joined to a doubly-bonded carbon, does not behave like an alkyl halide. Allyl bromide (page 90) which has halogen atom on a carbon once removed from a doubly-bonded carbon is, on the contrary, more reactive than the corresponding saturated compound. The same behavior has been noted in other similarly constituted aliphatic compounds.

Now in an aromatic nuclear halogen compound we have an arrangement similar to that of a vinyl halide (see I below)



and we should expect the lessened activity actually observed. (The loss of HX characteristic of vinyl halides cannot occur with the benzene ring.) A side-chain halide like benzyl chloride has an arrangement like allyl chloride (II above) and is correspondingly active. A compound with an arrangement like that of III shows no enhanced activity.

#### USES OF HALOGEN COMPOUNDS

Chlorobenzene is industrially important for manufacture of certain dyes and for the synthesis of phenol and of aniline. Both *o*- and *p*-dichlorobenzenes are insecticides, the latter being preferred. Bromobenzene is a valuable laboratory compound for Grignard and Fittig reactions. Benzyl and benzyldene chlorides are intermediates, used in industrial laboratory synthesis of benzaldehyde, esters, dyes, photographic developers. For interesting charts of syntheses from chlorobenzene see reference 3.

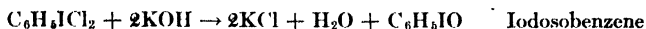
#### IODOSOBENZENE AND IODONIUM COMPOUNDS

These compounds have no great importance but they display interesting properties They were extensively investigated by Victor Meyer. Iodobenzene differs from chloro- and bromobenzene in forming derivatives in which the halogen is multivalent. These may be likened to such inorganic compounds as iodine trichloride,  $\text{ICl}_3$ , etc. Iodobenzene in chloro-

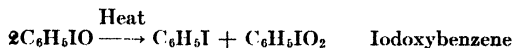
form solution reacts with chlorine to form phenyl iodoso chloride:



The latter may be converted to iodosobenzene by treatment with potassium hydroxide:



Iodosobenzene on being heated yields iodobenzene and iodoxybenzene (oxidation product of iodosobenzene).



This is an example of an intermolecular oxidation and reduction. Both iodosobenzene and iodoxybenzene are very unstable substances; both are oxidizing agents by virtue of the unnatural valence of the iodine atom.

Iodosobenzene mixed with iodoxybenzene and moist silver oxide yields diphenyl iodonium hydroxide:



The latter compound is remarkable in that it is a strong base, strictly comparable to the organic ammonium and sulfonium bases (page 309).

## REVIEW QUESTIONS

- Write equations showing how to prepare: (a) Chlorobenzene; (b) Iodobenzene; (c) *p*-Dichlorobenzene; (d) Benzyl chloride; (e) *p*-Tolyl chloride; (f) *p*-Chlorobenzyl chloride; (g) Benzylidene chloride. Describe each process briefly.
- Write two chemical names for each of the last four compounds named above.
- What reactions may be used to distinguish the following compounds from each other: (a)  $\text{C}_6\text{H}_5\text{CH}_2\text{Br}$  and  $\text{CH}_3\text{C}_6\text{H}_4\text{Br}$ ? (b)  $\text{C}_6\text{H}_5\text{CHCl}_2$  and  $\text{ClC}_6\text{H}_4\text{CH}_2\text{Cl}$ ?
- Write the formulas of the compounds which would result from the action of water, of ammonia, and of an oxidizing agent, upon: (a)  $\text{C}_6\text{H}_5\text{CH}_2\text{Cl}$ ; (b)  $\text{ClC}_6\text{H}_4\text{CH}_2\text{Cl}$ ; (c)  $\text{CH}_3\text{C}_6\text{H}_4\text{Cl}$ .
- By what means could the presence of bromine be demonstrated in the following compounds? (a)  $\text{CH}_3\text{C}_6\text{H}_3\text{Br}_2$ ; (b)  $\text{C}_6\text{H}_5\text{CHBr}_2$ .
- In direct chlorination of benzene which trichlorobenzene would probably form in smallest amount?
- Suppose you were trying the reaction indicated on page 431. Describe the tests you would make to prove whether or not the indicated reaction had taken place. Write equations for the tests (assume a positive result).
- Write equations for those reactions of bromobenzene which are shared by ethyl bromide.
- What physical and chemical traits are of use in the identification of an aryl halide?
- In what order should the reagents be used in making the following compounds from benzene? (a) *p*-Chloronitrobenzene; (b) *m*-Bromonitrobenzene; (c) *p*-Bromobenzene-sulfonic acid; (d) *p*-Bromotoluene.
- Complete the following equations.
  - $\text{C}_6\text{H}_5\text{CHCl}_2 + \text{KOH solution} \rightarrow$
  - $\text{C}_6\text{H}_5\text{CH}_2\text{Br} + \text{KCN} \rightarrow$
  - $\text{ClC}_6\text{H}_4\text{CH}_2\text{Cl} + \text{hot KMnO}_4 \text{ solution} \rightarrow$
  - $\text{C}_6\text{H}_5\text{CH}_2\text{Br} + \text{Mg (ether)} \rightarrow$
  - $\text{C}_6\text{H}_5\text{CH}_3 + \text{Cl}_2 \text{ (heat, sunlight)} \rightarrow$
- The compound (A) contains 66.4% C, 5.53% H, and 28.0% Cl. It does not appear to react with NaOH solution, but upon oxidation with permanganate solution it yields an acid (B) of m.p. 141–2°C. (B) contains 53.7% C, 3.20% H, 20.45% O, and 22.68% Cl. What is the structure of (A)?

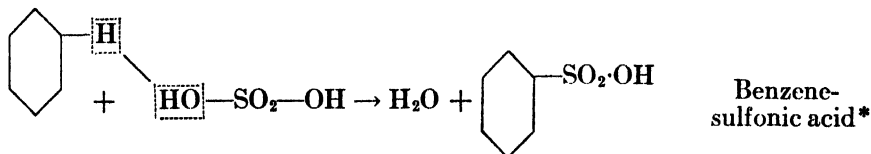
13. Compound (A) contains 52.18% C, 3.73% H, and 44.1% Cl. Upon reaction with dilute NaOH solution the compound (B) is secured. This contains 58.95% C, 4.91% H, 24.91% Cl, the balance being oxygen. Oxidation of (A) yields a monocarboxylic acid (C) of m.p., 242–3°C. A sample of (C) weighing 0.1565 g. will neutralize 11.05 cc. of 0.0905 N NaOH solution. What is the structure of (A)? Give complete proof.

## LITERATURE REFERENCES

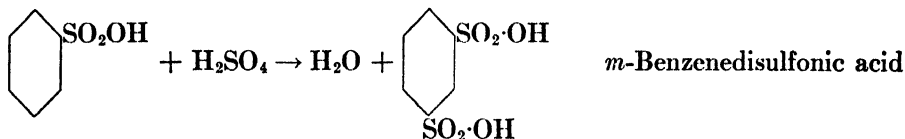
1. GROGGINS. *Unit Processes in Organic Synthesis*. McGraw-Hill Book Co., 1938, 153. (Halogenation.)
2. ELLIS. *The Chemistry of Petroleum Derivatives*. Chemical Catalog Co., 1934, 755. (Halogenation of benzene, etc.)
3. GUBELMANN. Relation of the dyestuff industry to other industries. *Ind. Eng. Chem.*, **27**, 618 (1935).
4. SAFFER and DAVIS. Products from the Wurtz reaction and the mechanism of their formation. *J. Am. Chem. Soc.*, **64**, 2039 (1942).
5. MORTON, DAVIDSON, NEWAY, and HAKAN. Condensations by sodium. General theory of the Wurtz reaction. *J. Am. Chem. Soc.*, **64**, 2240, 2242 (1942).
6. KHARASCH and BROWN. Chlorinations with sulfuryl chloride. I. The peroxide-catalyzed chlorination of hydrocarbons. *J. Am. Chem. Soc.*, **61**, 2142 (1939).

## SULFONIC ACIDS

**Preparation.** When sulfuric acid reacts with an aromatic hydrocarbon, a derivative is formed in which OH group of the acid is replaced by aryl radical with loss of water:



Ordinarily concentrated sulfuric acid or acid containing dissolved sulfur trioxide (fuming sulfuric acid) is employed for this process.† The reaction is known as *sulfonation*; the product, called a sulfonic acid, has  $\text{SO}_3\text{H}$  group substituted for nuclear hydrogen atom. As we shall see, the reaction of sulfonation has considerable importance in the aromatic series. By continuing the reaction, using a higher concentration of sulfuric acid and higher temperature, a disulfonic acid is formed:



Ready sulfonation is characteristic of the aromatic series; aliphatic saturated hydrocarbons are in general resistant to the action of sulfuric acid. The entrance of  $\text{SO}_3\text{H}$  group into the benzene ring is hindered by the presence of carboxyl group, but the presence of  $\text{NH}_2$ ,  $\text{OH}$ , or alkyl group favors the reaction. (See note, page 416.) The introduction of a second sulfonic group is made more difficult by the presence of the first (*meta*-directing, "hindering" group).

It should be distinctly noted that the sulfonic acids are not similar to such compounds as ethylsulfuric acid,  $\text{C}_2\text{H}_5\text{OSO}_2\text{OH}$  (Ethyl hydrogen sulfate) in which hydrogen of sulfuric acid has been replaced. Such a

\* This reaction is not to be interpreted as a double decomposition. The exact mechanism is unknown. One theory proposes that the acid first adds to benzene; water is then split off in a second step.

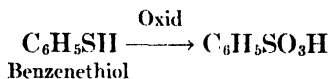
† In some cases chlorosulfonic acid,  $\text{ClSO}_3\text{H}$ , is used. In sulfonation of toluene this reagent gives a larger yield of *ortho* compound than can be had when sulfuric acid is used (see page 439).

substance is an ester, easily hydrolyzable. Sulfonic acids are to be compared with carboxylic acids:

$\text{RCO}_2\text{H}$ .....	Carboxylic acid
$\text{RSO}_3\text{H}$ .....	Sulfonic acid

They are strong acids; they have the sulfur atom directly connected to carbon, therefore they hydrolyze with difficulty.

Another method of forming a sulfonic acid depends upon the oxidation of a thiol:



This reaction confirms the statement that sulfur and carbon are directly joined in a sulfonic acid.

### PHYSICAL PROPERTIES

Most of the sulfonic acids are crystalline solids, quite water-soluble. Many are hygroscopic. In general the sulfonic acids do not possess sharp melting points, and they may not be distilled, as they decompose on being strongly heated. They have all the characteristics of strong acids, and under ordinary conditions are quite stable compounds. Their barium and calcium salts are water-soluble, in contrast to the behavior of sulfates.

**Isolation of Sulfonic Acids.** Because of their ready solubility in water, special methods are needed to isolate the sulfonic acids. (a) Following a sulfonation the excess sulfuric acid may be precipitated as barium sulfate by treatment of the mix with barium carbonate. Following filtration, the solution is treated with just enough sulfuric acid to precipitate the barium ion as barium sulfate, after which evaporation of the solution yields the sulfonic acid.\*

(b) The sodium salt of a sulfonic acid may usually be precipitated by pouring the sulfonation mix into cold concentrated brine.

**Uses.** Sulfonation is often resorted to because of the increased solubility in water which is conferred on the compound so treated. Thus many dyes are made soluble by introduction of  $\text{SO}_3\text{H}$  group. Excellent detergents and wetting agents (page 220) are made by the sulfonation of alkyl benzenes. The formula  $\text{RC}_6\text{H}_4\text{SO}_3\text{Na}$  illustrates this type of detergent; R is composed of from 12 to 18 carbon atoms.

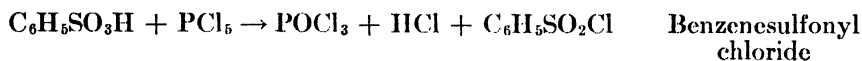
### REACTIONS

Sulfonic acids form the same types of derivatives (esters, amides, etc.) which have become familiar through our study of the carboxylic acids. In

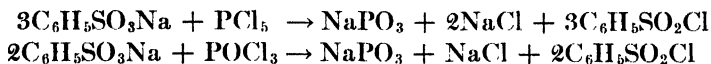
\* In commercial work lime is used, giving the soluble calcium sulfonate. This operation is known as "liming out." After removal of insoluble calcium sulfate by filtration, sodium carbonate is added to the filtrate; this gives insoluble calcium carbonate and leaves a solution of the sodium sulfonate, from which the water is evaporated to yield the solid sodium sulfonate.

general these derivatives are produced by the same reactions used with carboxylic acids. This similarity will be noted in the examples which follow.

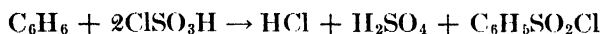
(1) *Acid Chloride*. Sulfonyl chlorides are formed by the action of  $\text{PCl}_5$  upon sulfonic acids:



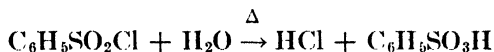
however, it is more practical to employ the salt of the acid in this reaction:



It is also feasible to prepare a sulfonyl chloride by the use of chloro-sulfonic acid:

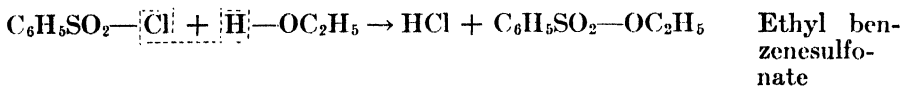


If the sulfonic acid is desired it may be obtained by hydrolysis of the acid chloride:

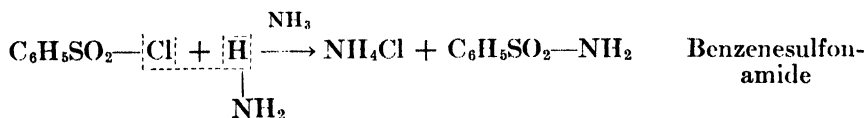


Benzenesulfonyl chloride is typical of aromatic sulfonyl chlorides. It is a liquid of characteristic and very disagreeable odor, having the chemical behavior of an aromatic acid chloride, such as benzoyl chloride. Its vapor is lacrymatory.

(2) *Esters and amides* of sulfonic acids are best made from the acid chloride as indicated in the following equations:

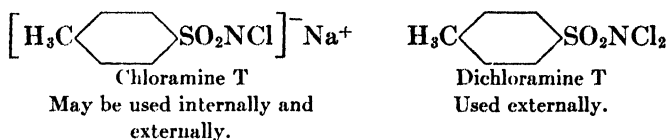


These esters when heated give olefins. Heated with alcohols, they yield ethers. There is less charring in either case than when sulfuric acid is employed.

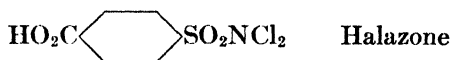


Amides of sulfonic acids may be crystallized from hot water. Like other amides they have definite melting points and serve to identify their acids.

When *p*-toluenesulfonamide is treated with sodium hypochlorite solution "positive" chlorine substitutes for hydrogen on the nitrogen atom. The resulting compound (sodium salt) is Chloramine T. The corresponding dichloro compound is Dichloramine T.



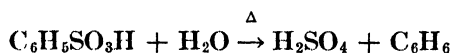
Both are surgical antiseptics. The former has 11.5–13% active Cl, the latter 28–30%. Halazone resembles Dichloramine T:



It is a powerful disinfectant, used like chlorine, for instance for sterilizing water.

#### REPLACEMENTS OF $\text{SO}_3\text{H}$ GROUP

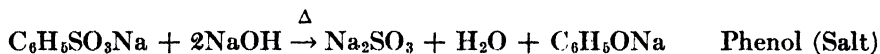
(1) *The hydrolysis of a sulfonic acid* by steam under pressure restores the hydrocarbon together with sulfuric acid:



(2) *By reduction of a sulfonic acid*, carried out upon its acid chloride, a thiol is formed; this is the reverse phase of the reaction shown before by which a thiol is oxidized to a sulfonic acid.

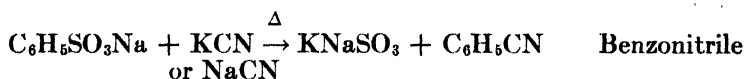
**Exchange Reactions.** The sulfonic acids or their salts participate in a number of metathetical reactions which resemble closely those of the alkyl halides. In the following cases the dry sulfonate salt is fused with another dry reagent. The reactions are illustrated in the following equations.

(1) *Fusion of the salt of a sulfonic acid with sodium hydroxide* yields a phenol:

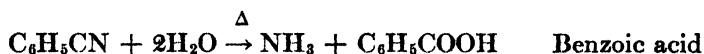


This reaction has considerable commercial importance for the production of phenol itself, and related compounds such as naphthols.

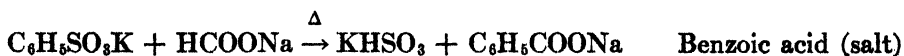
(2) *Action of sodium salt with potassium cyanide; formation of a nitrile:*



The hydrolysis of the nitrile leads to the corresponding carboxylic acid:

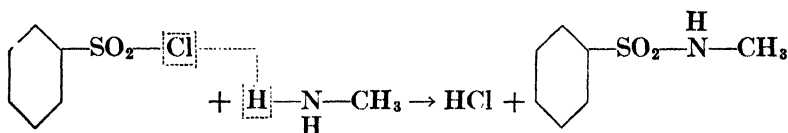


(3) *Action of potassium salt with sodium formate; formation of carboxylic acid:*

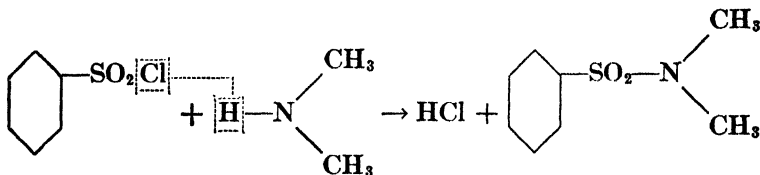
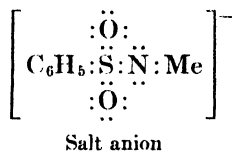


The yield here is not good but the reaction is sometimes useful. The two reactions illustrated show how the sulfonic group is transformed to carboxyl, and suggest methods of introducing carboxyl group into the benzene nucleus. It should, however, be noted that the above method for producing a nitrile is not as practical as the Sandmeyer reaction (presented on page 483).

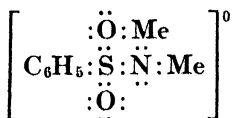
**Hinsberg Reaction.** The Hinsberg reaction is used to distinguish between primary, secondary, and tertiary amines (see page 471), and may also be used to separate each from a mixture. Benzenesulfonyl chloride is the reagent. It forms sulfonamides with primary and secondary amines, but has no such action upon tertiary amines. For illustration of the use of this reagent, its actions with methylamine (primary) and dimethylamine (secondary amine) are shown below:



This compound is soluble in NaOH solution, forming a salt.



This compound is not able to form a salt as it lacks mobile hydrogen atom. It is insoluble in NaOH solution.



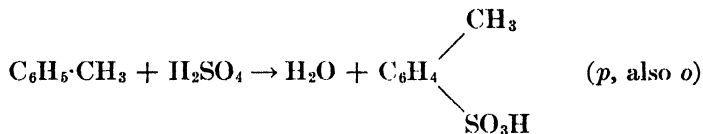
Benzenesulfonyl chloride does not react with tertiary amines, as the latter have no removable hydrogen atom (see reactions of amines, Chapter XVI). As suggested above, the primary and secondary amines may be separated by the action of sodium hydroxide solution upon their sulfonamides. The free primary and secondary amines are released on boiling the sulfonamides with sulfuric or hydrochloric acid.



## SULFONATION OF BENZENE HOMOLOGS

As has already been stated the reaction of sulfonation takes place more easily with benzene homologs than with benzene. The resulting compounds are similar to the benzenesulfonic acids in their reactions.

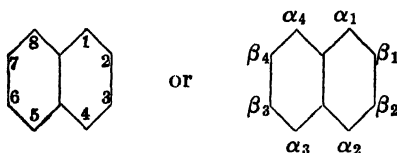
Example: Formation of toluenesulfonic acids:



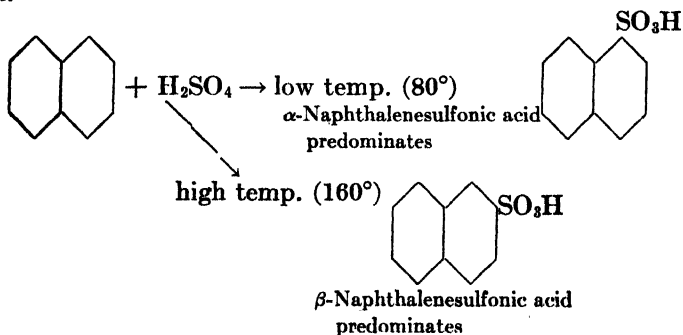
At water-bath temperature this reaction produces chiefly *p*-toluenesulfonic acid, while at room temperature the *ortho* compound predominates. *p*-Toluenesulfonyl chloride is sometimes used in the Hinsberg reaction in place of benzenesulfonyl chloride. Alkyl esters of *p*-toluenesulfonic acid may be used as alkylating agents.

## NAPHTHALENE SULFONIC ACIDS

Other aromatic nuclei besides benzene are, of course, subject to sulfonation, but in this book attention is confined largely to benzene compounds, because of lack of space for further discussion. However, the sulfonic acids of naphthalene deserve passing mention because of their great importance in the dye industry. The numbering system used with naphthalene is shown in the figure below, also another system in which the position of groups is indicated by the letters *alpha* ( $\alpha$ ) and *beta* ( $\beta$ ).



In the sulfonation of naphthalene the position taken by the  $\text{SO}_3\text{H}$  group is dependent upon temperature, low temperature favoring *alpha* substitution, while high temperature during the reaction increases the yield of *beta* compound.



Naphthalenesulfonic acids containing other groups, like  $\text{NH}_2$  or  $\text{OH}$  (mixed compounds) find wide employment for the making of dyes. The introduction of the sulfonic group into naphthalene has the effect of increasing the solubility of the compounds in water, as was also noted with the benzene compounds. This explains the sulfonation of dyes, which are often relatively insoluble in water.

### REVIEW QUESTIONS

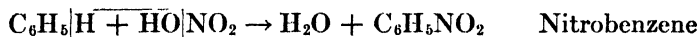
1. Write formulas for the products formed by the sulfonation of toluene, of chlorobenzene, of nitrobenzene, of benzenesulfonic acid.
2. What proof is there that the sulfur atom of benzenesulfonic acid is directly joined to the benzene nucleus?
3. Write equations for the reaction of *p*-toluenesulfonic acid with: (a)  $\text{PCl}_5$ ; (b)  $\text{EtOH}$ ; (c)  $\text{H}_2\text{SO}_4$ ; (d) An oxidizing agent; (e) Superheated steam.
4. What would be formed by the following treatment of the sodium salt of *o*-toluenesulfonic acid: (a) Fusion with an excess of  $\text{NaOH}$ ? (b) Reduction? (c) Reaction with  $\text{KCN}$ ? (d) Treatment of K salt with sodium formate?
5. Write graphic formulas of the compounds which would be produced by the action of benzenesulfonyl chloride upon: (a)  $\text{NH}_3$ ; (b) *p*-Toluidine; (c) Diethylamine. (d) Would any of these compounds dissolve in sodium hydroxide solution? If so why?
6. Show by equations the use of the Hinsberg reagent in distinguishing between propylamine, methylethylamine, and trimethylamine.
7. Why are dyes and other heavy molecules often sulfonated?
8. What indirect methods have we for introducing the sulfonic group into a ring?
9. Suggest a method for making halazone from *p*-toluenesulfonyl chloride.
10. How may a sulfonic acid be removed from a sulfonation mixture?
- (R)11. The sodium salt of compound (A) contains 43.3% C, 3.60% H, 24.74% O, 16.40% S, and 11.85% Na. Upon fusion with  $\text{KCN}$  it gives the compound (B) whose acid hydrolysis yields (C), which is an acid containing 70.6% C, 5.88% H, and 23.53% O. Molecular weight of (C) is 136. Oxidation of (C) gives an acid (D). When (D) is heated above its melting point, it loses water and passes to the compound (E). Compound (E) melts at  $130\text{--}1^\circ\text{C}$ . It contains 64.88% C, 2.70% H, and 32.43% O. Explain the reactions discussed and prove the structure of (A).

### LITERATURE REFERENCE

GROGGINS. *Unit processes in organic synthesis*. McGraw-Hill Book Co., 1938, 233. (Sulfonation.)

## NITRO COMPOUNDS

The industrial preparation of aliphatic nitro compounds is an accomplishment of recent years, as special means are necessary to produce them (page 297). The aromatic nitro compounds are more easily prepared and, as a consequence, they have been thoroughly studied. Many aromatic nitro compounds are valuable intermediates and many, such as nitrobenzene and polynitro compounds, have important direct applications. They are produced by interaction of a hydrocarbon or substituted hydrocarbon with nitric acid:



The reaction is termed nitration.\* As carried out in practice, concentrated sulfuric acid is generally mixed with the nitric acid to take up the water produced in the reaction and so prevent dilution of the nitric acid.† Though fuming nitric acid may be employed to raise the nitric acid concentration, the use of the cheaper sulfuric acid is an economical measure.‡

Nitration may also be carried out with sodium nitrate and sulfuric acid, or by the use of nitric acid in acetic acid or acetic anhydride. With these solvents nitric acid forms diacetyl *ortho* nitric acid,  $(\text{CH}_3\text{CO}_2)_2\text{N}(\text{OH})_2$ , which apparently is responsible for the nitrating action. Acetyl nitrate,  $\text{CH}_3\text{CO}_2\text{NO}_2$ , formed by action of  $\text{N}_2\text{O}_5$  upon acetic anhydride, is a valuable agent. It is used in solution in carbon tetrachloride or acetic anhydride, and has a tendency to nitrate in *ortho* position; this is frequently very much in its favor. Benzene may be nitrated to nitrobenzene in good yield by heating the vapor with nitrogen dioxide ( $310^\circ$ , silica gel catalyst).

Aliphatic saturated hydrocarbons are in general unaffected by nitric acid, except under extreme conditions, when oxidation may take place; while nitration is the rule with the aromatic hydrocarbons. It proceeds readily with benzene, and increasingly so with its homologs. The reaction is used in this way to tell one class of these hydrocarbons from the other.

\* The mechanism of the nitration reaction has not yet been determined with certainty. The equation given here is purely formal, that is it shows entering compounds and products, but not the "how" or the "why" of the reaction.

† The term *mixed acid* is often applied to a sulfuric-nitric acid mixture.

‡ If the nitric acid is allowed to become dilute, nitration will slacken or cease; moreover the dilute acid is far more likely to cause oxidation than is concentrated acid. Again, in some cases dilute acid causes substitution of nitro group on an alkyl side-chain. In certain cases the sulfuric acid affects the orientation of the nitro group. Thus nitration of acetanilide gives mainly the *p*-nitro compound, while nitration of aniline in sulfuric acid solution gives principally the *meta* compound. Nitration of acetanilide in carbon tetrachloride solution with acetyl nitrate gives a large yield of the *ortho* compound.

The introduction of a second nitro group into the benzene ring requires a higher temperature and more concentrated acid than is needed for the first group. The third group enters with still more difficulty, and not more than three nitro groups may be introduced by direct nitration. Nitration of the benzene ring is facilitated by the presence of OH, NH<sub>2</sub>, or CH<sub>3</sub> groups (*para* and *ortho* orienting groups); thus phenol is easily nitrated at room temperature by dilute nitric acid. Nitration is hindered by NO<sub>2</sub> group, SO<sub>3</sub>H, or CO<sub>2</sub>H (*meta* orienting), and also by the halogens.

### STRUCTURE OF NITROBENZENE

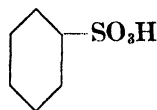
Nitrobenzene is a typical aromatic nitro compound, and the facts given below in proof of its structure apply as well to other nitro compounds.

(1) The nitrogen in nitrobenzene is attached to carbon of the ring, like the sulfur atom in a sulfonic acid. This contention is supported by the following facts:

(a) The compound is practically non-hydrolyzable, i.e., not an ester (C<sub>6</sub>H<sub>5</sub>ONO).

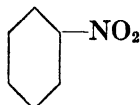
(b) Complete reduction of nitrobenzene gives aniline, C<sub>6</sub>H<sub>5</sub>NH<sub>2</sub>, an aromatic amine in which nitrogen is attached to carbon.

(2) Nitrobenzene is not an acid. It is formed in the same manner as benzenesulfonic acid, but there being only one OH group in nitric acid, its removal in the reaction also takes away the acidic properties of the compound. Sulfuric acid being dibasic, its benzene derivative retains one replaceable hydrogen. Note the formulas below:



Benzenesulfonic  
acid

One replaceable hydrogen remains.  
Compound acidic.



Nitrobenzene

Replaceable hydrogen lost in formation  
of compound. Non-acidic.

The formula shown above is the conventional one for nitrobenzene.

It is, however, incorrect to show this compound as C<sub>6</sub>H<sub>5</sub>N<sup>≡</sup>O with double bonds to each oxygen. Physical measurements show that the nitro group has but one double bond, the other oxygen being held by a coördinate link,

$\text{RN} \rightarrow \text{O}$ . Because of the resonance effect, the share of the oxygens in the double bond is identical (see page 398).

## PROPERTIES OF AROMATIC NITRO COMPOUNDS. USES

Nitrobenzene is a pale yellow liquid with a characteristic odor resembling almonds. Several other nitro compounds are liquids, but the series comprises solids for the most part. These are either colorless or pale yellow in color. Those compounds having  $\text{NH}_2$  or  $\text{OH}$  groups are sometimes orange-colored or red. These dissolve in alkali to give red or orange solutions. Mononitro compounds are volatile in steam.

Simple nitro compounds may usually be distilled; however, a multiplication of nitro groups leads to instability, and certain polynitro compounds decompose or explode when heated.

Their uses are mainly for chemical transformations. Several substituted nitro compounds are commonly used as explosives. Nitrobenzene, on account of its odor and general ability as a solvent, is used in metal polish, shoe polish, and has even been used in soaps. Its chief use is for the preparation of aniline. It is sometimes employed as an oxidizing agent.

A number of nitro compounds have strong and peculiar odors. Several with the tertiary butyl group have the odor of musk and are used in perfumery. To this group belong: trinitro-*tert*-butyl-toluene; 2,4,6-trinitro-5-*tert*-butyl-*metaxy*lene; 1-methyl,2,4-dinitro-3-methoxy-6-*tert*-butylbenzene; 4,6-dinitro-2,3,5-trimethyl-*tert*-butylbenzene.

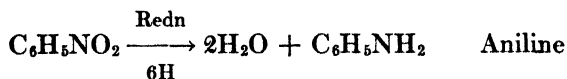
Nitrobenzene is an active poison. The vapor should not be inhaled, nor should any of the liquid be allowed to remain in contact with the skin. Nitro and polynitro compounds in general are poisonous. The latter often cause severe skin irritation. During the First World War 7000 cases of T.N.T. poisoning with 105 fatalities were reported from a single plant in a period of 20 months. Thousands of cases of poisoning by nitro compounds were similarly reported in 1942.

## REACTIONS OF NITRO COMPOUNDS

We will first consider the mononitro derivatives, of which nitrobenzene may serve as a type. Derivatives of such compounds are formed by substitution; however the most important reaction of nitro compounds is their complete reduction, by which amines are formed. The aromatic amines are exceptionally useful compounds for synthetic work, hence their production from the nitro compounds assumes first importance among the transformations of the latter substances. By partial reduction of the nitro compounds intermediate reduction products may be made, some of which have importance.

The degree of reduction of nitrobenzene is regulated by control of hydrogen ion concentration and the nature of the reducing agent.

(1) In acid solution complete reduction of nitrobenzene takes place; aniline is produced:



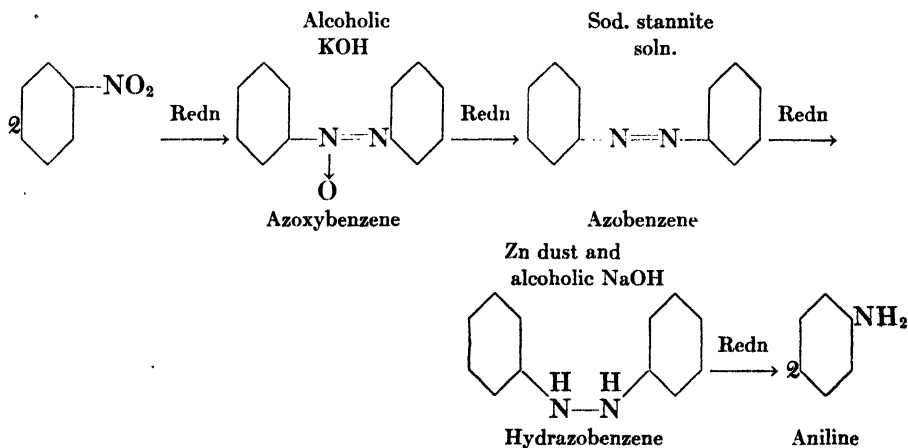
In the laboratory production of aniline from nitrobenzene, tin and hydrochloric acid are commonly used. In commercial operations iron and dilute hydrochloric acid are used. Aniline is further discussed in Chapter XXIV.

(2) In a neutral solution partial reduction takes place to form phenylhydroxylamine:



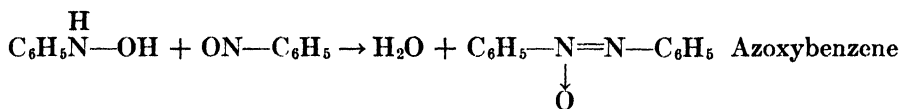
Dilute acid converts the hydroxylamine compound to *p*-aminophenol (see "rearrangements," page 473), while mild oxidation gives nitrosobenzene,  $\text{C}_6\text{H}_5\text{NO}$ . It will be observed that nitrosobenzene is an intermediate compound in the reduction of nitrobenzene to phenylhydroxylamine. It is, however, impossible to isolate this compound, since it reduces more rapidly than does nitrobenzene. However its presence in the reduction mixture has been shown by indirect means. Reduction passes this stage to produce phenylhydroxylamine, which may then be oxidized back to nitrosobenzene if this compound is desired. Another example of this method of gaining an intermediate reduction compound is found on page 356 under "Fructose to Glucose."

(3) In alkaline solution several compounds are formed in which two benzene rings are joined by partially reduced nitrogen. The agents used to produce these intermediate reduction products from nitrobenzene are shown in each case directly over the formula of the substance in the following series:

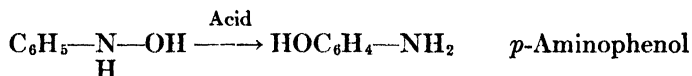


\* The capital N in the name indicates substitution of phenyl group on the nitrogen, not on oxygen. The *beta* indicates the same thing.

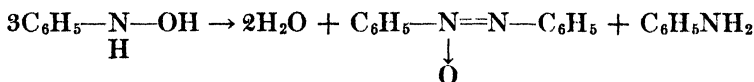
**Secondary Reduction Products of Nitrobenzene.** The formation of these bimolecular products is due to the reactivity of nitrosobenzene and phenylhydroxylamine. These by various combinations yield the above "secondary" reduction products. Thus, reaction of phenylhydroxylamine and nitrosobenzene gives azoxybenzene:



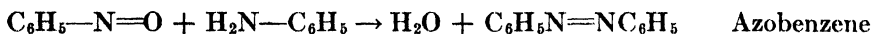
Whereas phenylhydroxylamine shifts to *p*-aminophenol in acid solution:



in alkaline media it undergoes mutual oxidation and reduction to azoxybenzene and aniline:



Hydrazobenzene may be oxidized to azobenzene by unreduced nitrobenzene, or the azobenzene may be formed as follows:

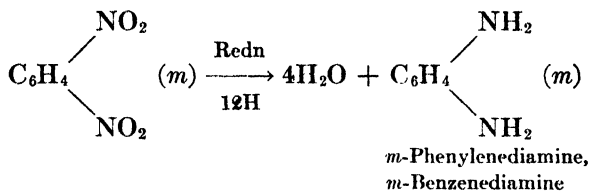


The final reduction product in alkaline solution is aniline. Hydrazobenzene, the intermediate directly before aniline, when treated with acid undergoes a shift, changing to the compound benzidine (see page 679). The latter is used in the formation of a type of dye and has other chemical uses which make it important. *p*-Aminophenol also has some importance (see page 510). Azoxybenzene and azobenzene have lesser importance.

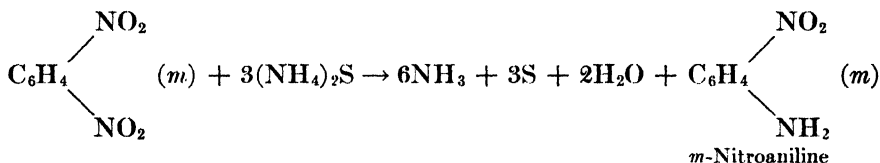
**Electrolytic Reduction.** The reduction of nitrobenzene, as well as the reduction of many other organic compounds, is very effectively carried out by the use of the electric current. This method is used for *p*-aminophenol. Nitrobenzene is reduced electrolytically in sulfuric acid. The phenylhydroxylamine then rearranges to *p*-aminophenol immediately as it is formed. The electrolytic method has obvious advantages in that extraneous chemicals are avoided. It is often susceptible of better control than would be possible in a chemical oxidation or reduction. A drawback is the insolubility of organic compounds in water and their general refusal to act as electrolytes. This makes necessary the addition of inorganic electrolytes, which may possibly react at a lower potential than is required for the organic compounds present, or may react in a detrimental manner with the organic compounds.

## REACTIONS OF DINITROBENZENES, ETC.

**m-Dinitrobenzene.** (1) *Reduction.* The complete reduction of a dinitro compound yields a diamine. Thus from *m*-dinitrobenzene *m*-phenylenediamine is secured:

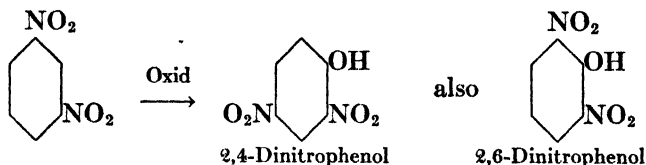


It is possible to reduce but one of the nitro groups of this compound by using ammonium sulfide as reducing agent. A nitroamine results from this action:

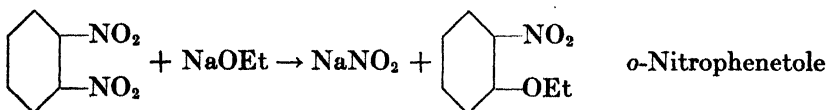


Alcoholic stannous chloride may also be used to reduce one nitro group when two are present.

(2) The hydrogens which are *ortho* or *ortho-para* to the two nitro groups of *m*-dinitrobenzene are easily displaced by oxidation (but not by substitution). We find oxidation occurring readily at this point. In this way dinitrophenols are formed:



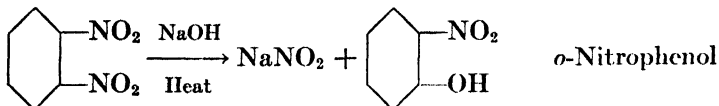
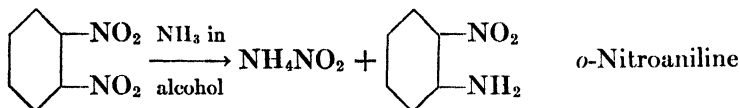
**Reactions of o-Dinitrobenzene.** A second nitro group introduced into *para* or *ortho* position to one already in the ring is loosely held, and may under certain conditions be removed. Thus *ortho*-dinitrobenzene, when treated with sodium ethoxide in alcohol, yields *o*-nitrophenetole:



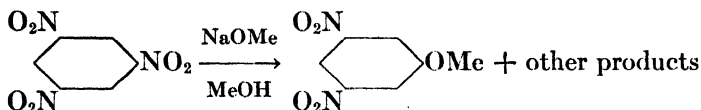
The *para* compound also shows this reaction but it is in general less reactive



than *o*-dinitrobenzene.\* The following equations show how the *o*-dinitro compound may be transformed to *o*-nitroaniline and *o*-nitrophenol:



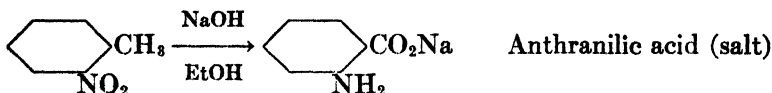
**Trinitrobenzene.** When two nitro groups are *meta* to a third it is loosely held. The situation resembles that in which one nitro group is *ortho* or *para* to another. 1,3,5-Trinitrobenzene, with alcoholic sodium methoxide, loses a nitro group:



When nitrobenzene is heated with solid potassium hydroxide it yields *o*- and *p*-nitrophenol. This reaction, and those which have been given above, show that while nitro group commonly activates the *meta* position, it can on occasion activate the *ortho* and *para* positions. An explanation is offered by the electronic theory of substitution which is reserved for the advanced course in organic chemistry. See also page 495.

**Molecular Compounds.** Certain polynitro compounds (picric acid, trinitrobenzene) unite with aromatic hydrocarbons to form molecular compounds. Many of these are quite unstable, but some are sufficiently stable to show definite melting points. Thus the picrates of certain hydrocarbons (naphthalene, anthracene, etc.) may be used in identification of these substances.

**Internal Oxidation by Nitro Group.** As said before nitrobenzene is an oxidizing agent. Interesting cases are known in which the reduction of the nitro group is caused by another group of the same molecule. For instance, *o*-nitrotoluene when heated with alcoholic sodium hydroxide solution is converted to anthranilic acid (salt):



\* When two like groups are found on a benzene ring, the influence of one group upon the other is usually greatest when they are *ortho* and least when they are *meta* to each other. The nitro group usually exerts a pronounced influence upon other groups substituted on the same ring. An example was given on page 438 and others will be given later.

## SCHEME OF REACTIONS OF NITROBENZENE

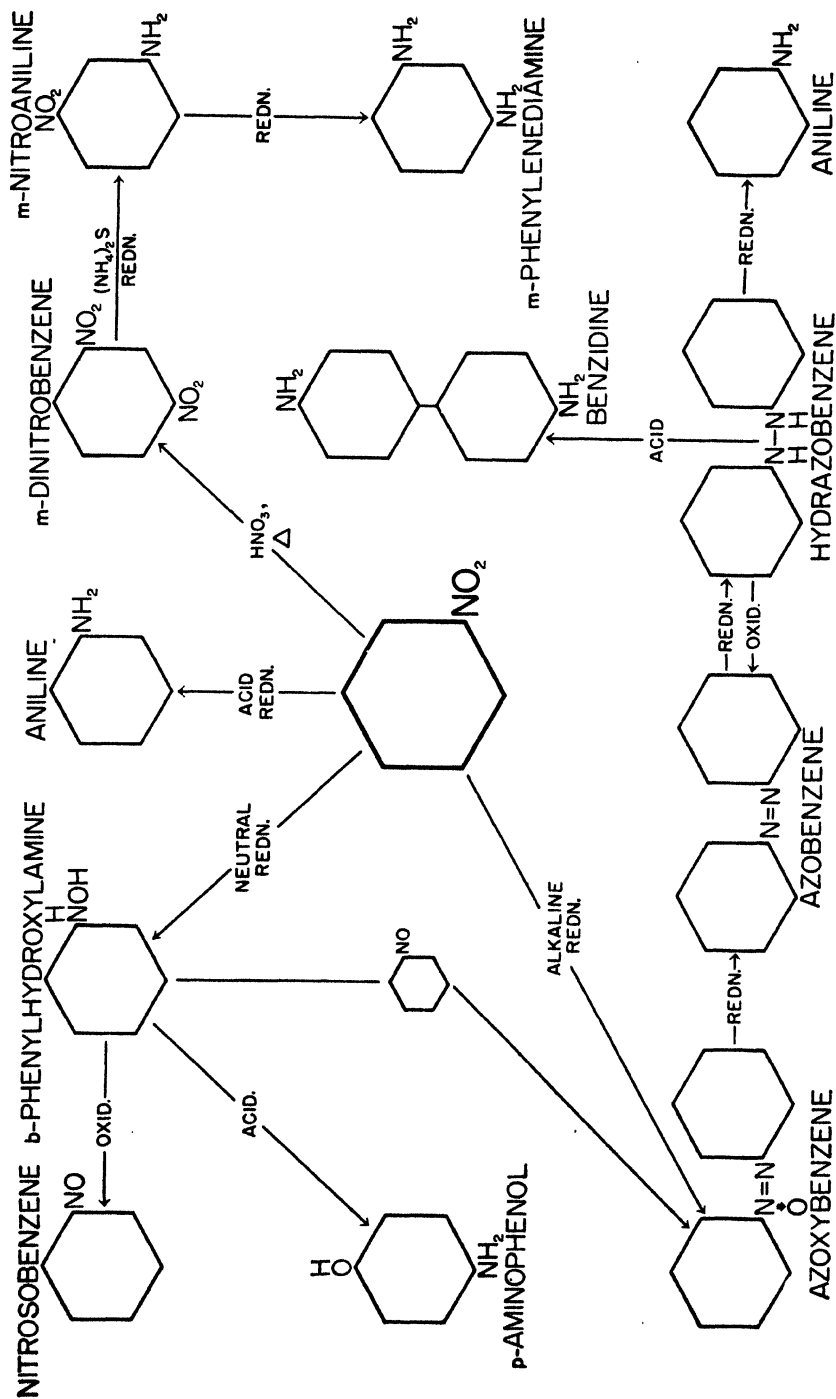
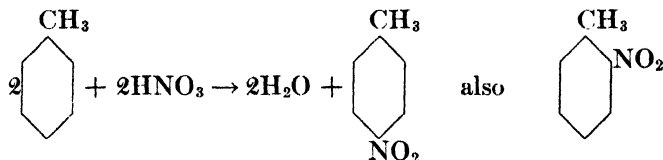


CHART VIII.

The chart of reactions of nitrobenzene on page 451 summarizes the most important transformations of this compound.

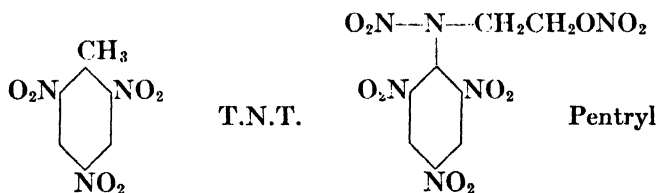
### NITRATION OF BENZENE HOMOLOGS. EXPLOSIVES

The behavior of toluene towards nitric acid characterizes that of other benzene homologs. Its nitration yields *p*- and *o*-nitrotoluenes:

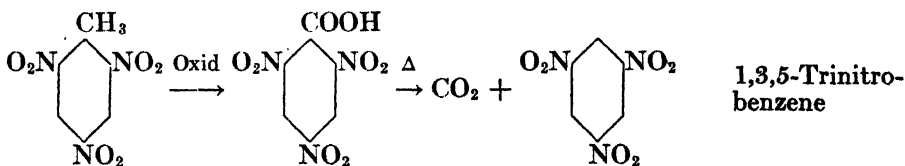


Continued nitration produces finally trinitrotoluene.

**Explosives.** The explosive nature of polynitro compounds has already been mentioned. Trinitrotoluene has a wider use as an explosive than any other of the aromatic nitro compounds. It is a reasonably safe explosive, requiring strong detonation to set it off. In its manufacture toluene is nitrated in three stages to the trinitro compound. Impurities which are present at the end of nitration include dinitrotoluene, trinitrobenzene, and isomers of T.N.T. which result from the further nitration of *m*-nitrotoluene. A detailed description of the removal of these impurities will be found in Reference 9, page 455.

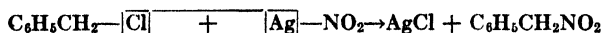


Trinitrobenzene is most explosive of the nitrated aromatic hydrocarbons. It is very difficult to prepare this compound by direct nitration of benzene. It is made from T.N.T. by oxidation of the methyl group. This gives trinitrobenzoic acid, which in the hot reaction mixture loses carbon dioxide.

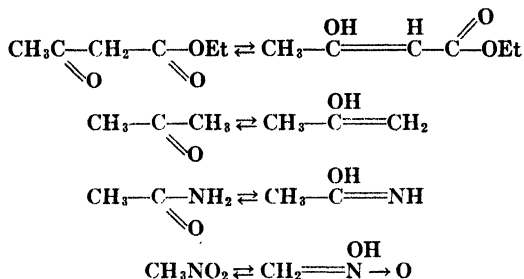


Other nitrated aromatic hydrocarbons used as explosives are: *m*-dinitrobenzene, trinitro-*m*-xylene, pentryl, hexanitrobiphenyl, nitrated naphthalenes. For other explosive compounds, see "Explosives" in the index, also page 475.

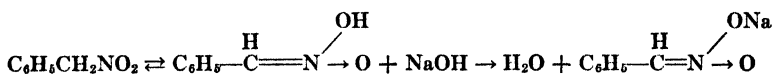
**Phenylnitromethane.** The compound phenylnitromethane,  $\text{C}_6\text{H}_5\text{CH}_2\text{NO}_2$ , is isomeric with the nitrotoluenes, but of a totally different chemical character, being aliphatic in nature. It is prepared from benzyl chloride and silver nitrite:



In aliphatic compounds containing nitro group the hydrogen on adjacent carbon is "active" (loosely held) as we find it in aldehydes, ketones, etc. (see page 298). The same behavior may be expected whenever we have hydrogen on carbon next to a doubly-bound atom. Note the following examples:



All such compounds undergo keto-enol tautomerism, by reason of which they become acidic, the loosely bound hydrogen being easily removed. Phenylnitromethane shows these properties also, forming salts with bases.

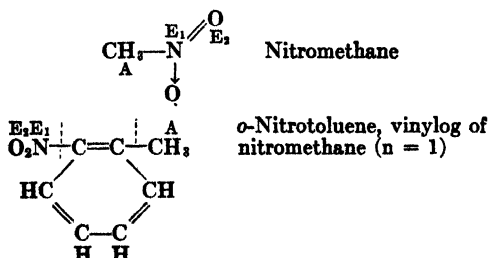


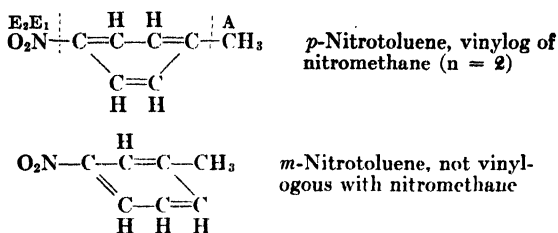
Phenylnitromethane in its nitro form is a yellow oil of boiling point  $226^\circ$ . It dissolves slowly in a base to give a salt of the acid form. If carbon dioxide is passed into the solution the yellow oil reforms, but if the solution is chilled and treated with a mineral acid, a white solid of melting point  $84^\circ$  is obtained. This is the acid form which dissolves rapidly in base; upon standing it changes to the nitro form. The solid form colors ferric chloride solution (test for OH group); the liquid does not.

**Vinylogy.** The principle of vinylogy states (in part) that when in a compound of the type  $\text{A—E}_1\text{=E}_2$  a structural unit of the type  $\left[ \begin{array}{c} \text{C}=\text{C} \\ | \quad | \end{array} \right]_n$  is interposed between A and  $\text{E}_1$ , the func-

tion of  $\text{E}_2$  remains unchanged, but that of  $\text{E}_1$  may be usurped by the carbon atom attached to A. A series of compounds built up in this way with various values of  $n$  is called a *vinylogous series*, the members being *vinylogs* of one another. This principle is frequently useful.

For example, the hydrogen atoms of nitromethane are easily removed in condensations with aldehydes. Similar reactions are noted with derivatives of toluene, and these are rational in view of the fact that nitromethane is vinylogous with the toluene compounds.

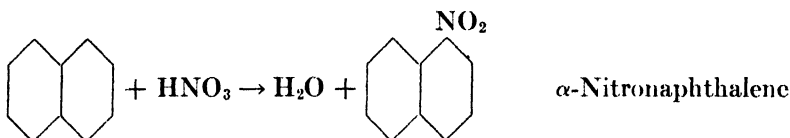




The  $\text{CH}_3$  group of *o*- and *p*-nitrotoluenes is active, that of *m*-nitrotoluene is not. Many other cases which illustrate the principle are known, for mention of which Reference 5 should be consulted.

### NITRATION OF NAPHTHALENE

The *alpha* nitro compound is formed by direct nitration. It is a yellow solid.



Continued nitration introduces nitro groups in positions 5 or 8, therefore *beta*-nitronaphthalene is prepared in other ways (see page 588). Dinitro-, trinitro-, and tetranitronaphthalenes are known. The latter explode on being heated.

### REVIEW QUESTIONS

1. Give reasons for concluding that the nitrogen atom of nitrobenzene is directly attached to carbon of the nucleus.
2. Give equations for the reactions by which the following substances may be made from nitrobenzene: (a) Phenylhydroxylamine; (b) Nitrosobenzene; (c) Azoxybenzene; (d) Hydrazobenzene; (e) Aniline.
3. Write equations showing the formation of the following compounds from benzene: (a) *m*-Nitroaniline; (b) *m*-Phenylenediamine; (c) 2, 6-Dinitrophenol; (d) *o*-Nitroaniline; (e) *o*-Nitrotoluene; (f) *m*-Bromonitrobenzene; (g) *p*-Chloronitrobenzene.
4. How does the behavior of phenylnitromethane contrast with that of *m*-nitrotoluene?
5. Write graphic formulas for the substances which would be formed by the action of nitric acid upon: (a) Bromobenzene; (b) Benzenesulfonic acid; (c) *m*-Dinitrobenzene; (d) *o*-Nitrophenol.
6. Discuss the tautomerism of phenylnitromethane.
7. Write graphic formulas for the artificial musks listed on page 446.
8. Account for the importance of nitrobenzene and other aromatic nitro compounds.
9. Name the primary reduction products of nitrobenzene; account for the formation of secondary reduction products from them.
10. Discuss the means to be employed to obtain either *ortho*, *meta*, or *para* nitroaniline in good yield.
11. By proper treatment of benzidine the  $\text{NH}_2$  groups may be removed and biphenyl may be made. Benzidine may also be made by proper treatment of *p*-nitrochlorobenzene. Write equation for this synthesis. Show how these syntheses establish the accepted structural formula for benzidine.

12. State clearly the evidence obtained in a test-tube reaction (in which benzene is warmed with concd.  $\text{H}_2\text{SO}_4$  and concd.  $\text{HNO}_3$ ) which shows that a nitro compound has formed.
13. In making nitrobenzene from benzene how could one tell that the reaction was complete? (Describe the test briefly.)
14. Give physical and chemical data which allow one to distinguish a solid sulfonic acid from a solid nitro compound.
15. Nitrobenzene has been used in soaps, in perfumes, and in shoe dyes. Discuss the advisability of such uses for the compound.
16. Outline the methods which may be used to prepare aromatic nitro compounds.
17. The compound (A) contains 61.3% C, 5.11% H, 23.35% O, and 10.22% N. Upon complete reduction (B) is produced; this is a liquid of b.p.,  $199 \pm 1^\circ\text{C}$ ., containing 13.08% N. Oxidation of (A) with nitric acid yields a monocarboxylic acid (C) of m.p.,  $147^\circ\text{C}$ . (C) contains 50.3% C, 3.0% H, 38.33% O, and 8.38% N. What is the structure of (A)?

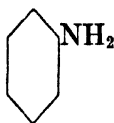
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## AROMATIC AMINES

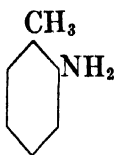
It has already been shown in Chapter XVI that the amines are derivatives of ammonia,  $\text{NH}_3$ , in which organic radicals replace one or more of the three hydrogen atoms. In the aromatic amines, aryl groups are exchanged for hydrogen atoms of the mother substance. Like the other substitution products of benzene, they fall into two groups. In one of these the nitrogen atom of ammonia is directly joined to the benzene nucleus, while in the other it finds attachment to carbon of a side-chain. The former class includes:

(1) *Primary Amines*. These are conveniently divided into monamines, diamines, etc. Aniline (aminobenzene) is an example of an aromatic primary monamine:

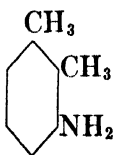


Aniline, aminobenzene, or phenylamine

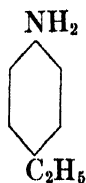
Homologs of aniline include the toluidines (*o*, *m*, *p*) and the xylidines, etc.



*o*-Toluidine

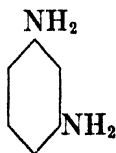


*o*-Xylidine



*p*-Amino-ethylbenzene

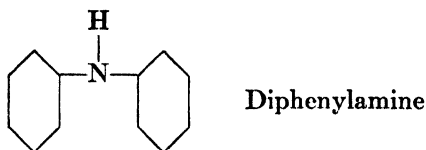
Derivatives of benzene with from two to six amino groups are known. Of these compounds the phenylenediamines (*o*, *m*, *p*) are the most useful:



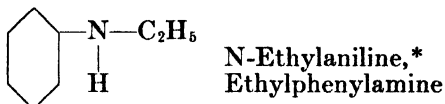
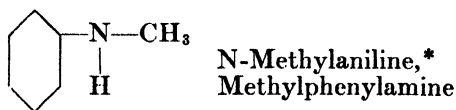
*m*-Phenylenediamine,  
*m*-Benzenediamine

Compounds like aniline, the toluidines, etc., shown above are true amines, yet as will be shown in later sections, they differ considerably in their reactions from the aliphatic amines. Some chemists for this reason prefer for them the name *amino-compounds*.

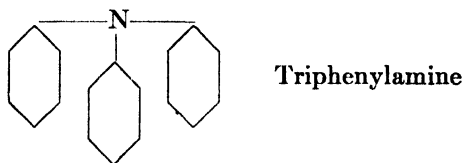
(2) *Secondary Amines*. This group includes *simple* aromatic amines like diphenylamine:



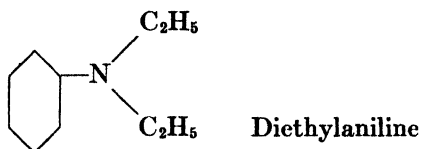
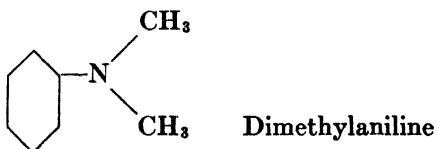
also *mixed* aliphatic-aromatic amines, of which the following substances are examples:



(3) *Tertiary Amines.* Triphenylamine typifies a simple aromatic tertiary amine:

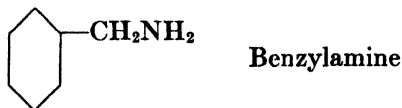


while dimethylaniline and diethylaniline are examples of mixed aliphatic-aromatic tertiary amines:



Compounds of the latter type are more important for chemical work than the simple tertiary aromatic amines.

The second class of amines mentioned in the opening paragraph includes such compounds as benzylamine:



which, as might be expected, are quite similar in reactions and in mode of formation to the aliphatic amines studied in Chapter XVI. The nuclear amino compounds are of vastly greater importance than are those of the type of benzylamine; chief interest attaches to primary monamino com-

\* See footnote, page 447.



pounds, of which aniline is a type substance. The importance of this compound in organic synthesis may be judged from the number of applications to be found in the ensuing pages. Its chief uses lie in the dye and drug fields. Primary diamines and mixed aliphatic-aromatic tertiary and secondary amines follow aniline in importance.

### PHYSICAL PROPERTIES OF AMINES

Aniline and *o*- and *m*-toluidine are liquids, colorless when freshly prepared, but changing in time to dark brown or red, probably by reason of oxidation. All have a peculiar, though not disagreeable odor which, however, does not resemble that of ammonia. *p*-Toluidine and several of the xylidines are solids at room temperature. Primary amines may be distilled without decomposition. They are rather insoluble in water, but are soluble in the common organic solvents.

TABLE 36.—PHYSICAL CONSTANTS OF AMINO COMPOUNDS

Name	Formula	M.p., °C.	B.p., °C.	Sp. g., 20°/4°	K <sub>B</sub>
Aniline	C <sub>6</sub> H <sub>5</sub> NH <sub>2</sub>	— 6.2	184.4	1.022	5.4 × 10 <sup>-10</sup>
Toluidine ( <i>o</i> )	CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> NH <sub>2</sub>	— 16.3	200.7	0.998	3.3 × 10 <sup>-17</sup>
Toluidine ( <i>m</i> )		— 31.5	203.3	0.989	6.5 × 10 <sup>-1</sup>
Toluidine ( <i>p</i> )		44–5	200.5	0.973 <sub>50</sub> <sup>50</sup>	1.3 × 10 <sup>-9</sup>
Xylidine (2,3)	(CH <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> NH <sub>2</sub>	< — 15	223.8	0.992	
Xylidine (2,4)			213–4	0.978	
Xylidine (2,5)		15.5	213	0.980	
Xylidine (2,6)			216.9	0.979	
Xylidine (3,4)		49	226	1.076 <sup>17.5</sup>	
Xylidine (3,5)			221–2	0.972	
Phenylenediamine ( <i>o</i> )	C <sub>6</sub> H <sub>4</sub> (NH <sub>2</sub> ) <sub>2</sub>	103–4	256–8		3.3 × 10 <sup>-10</sup>
Phenylenediamine ( <i>m</i> )		62.8	284–7	1.139 <sub>15</sub> <sup>15</sup>	
Phenylenediamine ( <i>p</i> )		140	267		
N-Methylaniline	C <sub>6</sub> H <sub>5</sub> NHCH <sub>3</sub>	— 57.0	195.7	0.989	2.1 × 10 <sup>-10</sup>
N-Ethylaniline	C <sub>6</sub> H <sub>5</sub> NHC <sub>2</sub> H <sub>5</sub>	— 63.5	204.00	0.963	1.05 × 10 <sup>-9</sup>
Dimethylaniline	C <sub>6</sub> H <sub>5</sub> N(CH <sub>3</sub> ) <sub>2</sub>	2.5	193.0	0.956	1.3 × 10 <sup>-9</sup>
Diethylaniline	C <sub>6</sub> H <sub>5</sub> N(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub>	— 34.4	216.00	0.934	2.7 × 10 <sup>-8</sup>
Diphenylamine	(C <sub>6</sub> H <sub>5</sub> ) <sub>2</sub> NH	53	302	1.159 <sub>20</sub> <sup>20</sup>	
Triphenylamine	(C <sub>6</sub> H <sub>5</sub> ) <sub>3</sub> N	126.5	365	0.774 <sub>20</sub> <sup>0</sup>	
α-Naphthylamine	C <sub>10</sub> H <sub>7</sub> NH <sub>2</sub>	50	301	1.171 <sub>20</sub> <sup>20</sup>	9.9 × 10 <sup>-11</sup>
β-Naphthylamine		111–2	306.1	1.061 <sup>98</sup>	2 × 10 <sup>-10</sup>
Benzylamine	C <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> NH <sub>2</sub>		184.5	0.982	2.4 × 10 <sup>-5</sup>

The diamines are colorless solids, which upon exposure to the air take on color. Like monamines they distil without undergoing decomposition. They are in general more water-soluble than the monamino compounds.

Diphenylamine and triphenylamine are solids, the former having an agreeable odor. Both are insoluble in water but are soluble in alcohol, ether, etc.

Methyl- and ethylaniline, dimethylaniline, and diethylaniline are liquids which resemble aniline somewhat in odor. They are colorless when prepared, but darken with exposure to air and light. They distil without decomposition.

Aniline and similar compounds are quite toxic. One should not allow these compounds to stay on the skin and should avoid inhaling their vapors.

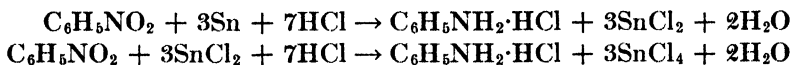
Benzylamine is a liquid. It differs from the true aromatic amines in that it is freely soluble in water. Table 36 presents melting points, boiling points, and densities of representative amino compounds.

### PREPARATION OF AMINES

(1) *Primary Amines.* The formation of primary amines by the action of ammonia upon a halogen compound, although possible for the aliphatic amines, can only be employed as a preparation method in the aromatic series by the use of special means, as the halogen atom of an aryl halide is firmly attached to the carbon nucleus. Because of the high temperature and pressure which are necessary, the reaction could not be used until the problems in construction of high pressure equipment had been solved. The preparation of aniline is now successfully carried out by heating chlorobenzene with 4-6 moles of concentrated ammonia, in presence of cuprous oxide and cuprous chloride, at a temperature of about 200° and a pressure of about 60 atmospheres.

Primary monamines and diamines are commonly prepared by the direct reduction of the corresponding aromatic nitro compounds. Thus aniline is formed when nitrobenzene is completely reduced.

In the laboratory, the customary reagents for reduction of nitrobenzene to aniline are tin and hydrochloric acid.



Under these conditions the aniline is secured as a salt, combined with hydrogen chloride and stannous or stannic chloride:

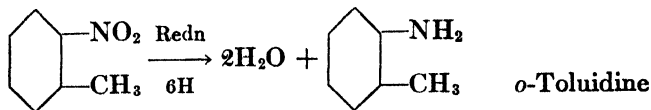


These double-salts are decomposed by the addition of an excess of sodium hydroxide, and the aniline is separated from the mixture by distillation with steam. The distillate of water and aniline is extracted with ether and the extract is dried, after which the ether is removed by a distillation. The resulting aniline is redistilled for final purification.

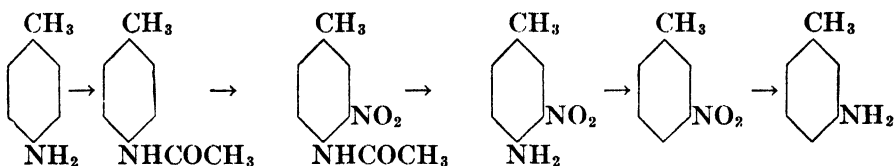
Commercially, aniline is still prepared by the reduction of nitrobenzene with iron and dilute hydrochloric acid. About one-fortieth of the amount of hydrochloric acid called for by the formal equation is used. This is

possible because water acts upon iron in the presence of ferrous chloride, generating hydrogen.\*

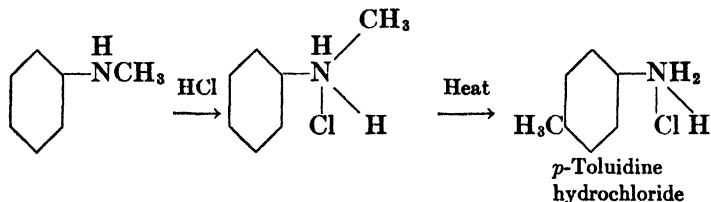
Homologs of aniline result from the reduction of their corresponding nitro compounds. The following equation shows the formation of *o*-toluidine from *o*-nitrotoluene by reduction:



*m*-Toluidine is made from *p*-toluidine. This is first acetylated, then nitrated. The acetyl group is removed by hydrolysis, then the *para* amino group is removed through the diazo reaction (page 482), after which the *meta* nitro group is reduced.



**Hofmann-Martius Reaction.** Another method makes use of the tendency of alkyl derivatives of aniline to "rearrange" when treated in special ways. When methylaniline is treated with hydrochloric acid in a closed container at 300°, the methyl group leaves the nitrogen atom and migrates to the *para* carbon atom of the nucleus. The hydrogen which is displaced from the nucleus goes to the nitrogen:

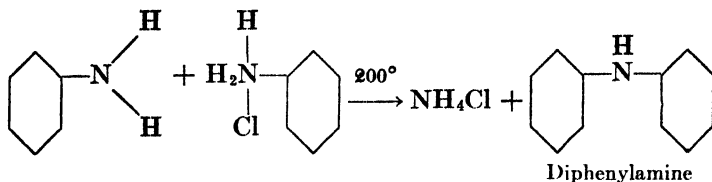


By means of this curious reaction *para* amino derivatives of the benzene homologs may be made. In some cases *ortho* compounds also result, but *meta* derivatives cannot be made by this method. Rearrangements of this type are taken up more fully later.

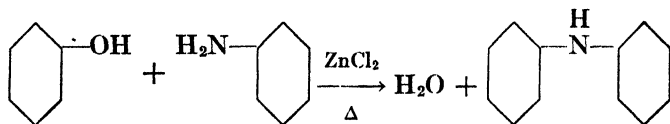
The reduction of the dinitrobenzenes yields the corresponding diamines. (See equation on page 449.)

\* Other methods used to introduce amino group to a ring, which cannot be discussed here are: (1) reduction of nitro group with various metals with acids, (2) catalytic reduction with nickel and hydrogen, (3) reduction with metals and salts, (4) replacement of hydroxyl by amino group, (5) replacement of CONH<sub>2</sub> by NH<sub>2</sub> through the Hofmann reaction, (6) direct replacement of NO<sub>2</sub> by NH<sub>2</sub> (see page 450).

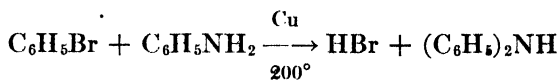
(2) Secondary and tertiary amines are produced as follows. Diphenylamine is made by interaction of aniline and an aniline salt:



This compound may be made from aniline and phenol, in the presence of a reagent which absorbs water:

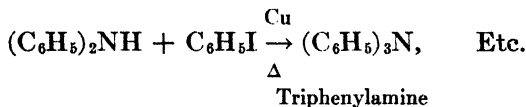


In presence of finely divided copper an aryl halide will react with an aromatic amine (Ullmann reaction):



Diphenylamine is used as a stabilizer for explosives (page 382) also in dye making. When dissolved in sulfuric acid it gives a deep blue color with oxidizing agents. Methods for the estimation of nitrous acid and of ferrous iron are based on this behavior.

Triphenylamine is formed when phenyl iodide and diphenylamine react in the presence of copper powder, used as a catalyst:

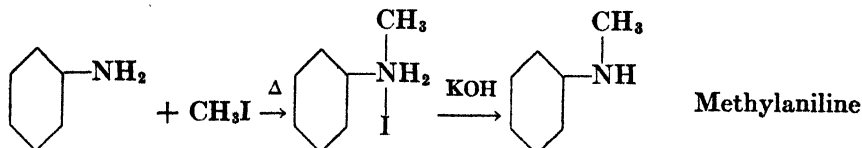


Or:

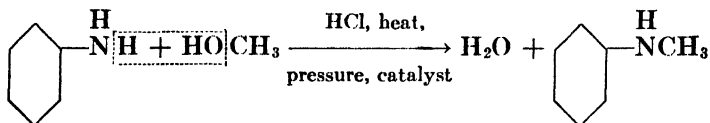


(3) Several methods may be used in preparing the mixed aliphatic-aromatic secondary and tertiary amines.

(a) The reaction of aniline with an alkyl halide gives a salt of a secondary mixed amine, from which the amine is recovered after treatment with a base:

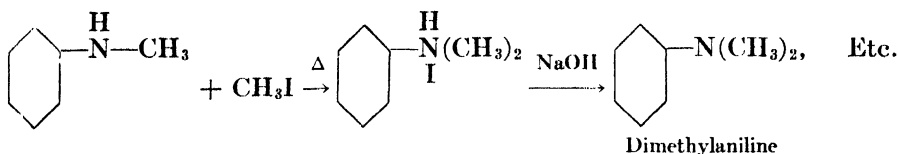


(b) The reaction of aniline with an alcohol in the presence of hydrochloric acid (or treatment of aniline hydrochloride with the alcohol) also produces a secondary amine:

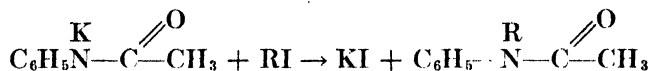


It is likely that the alkyl halide,  $\text{RCl}$ , is formed first, and that this reacts with the aniline in a second step.

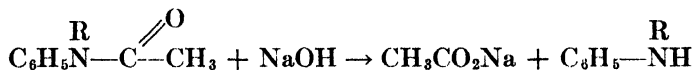
The dialkyl derivatives are prepared when additional alkyl halide or alcohol is employed in carrying out the reactions shown above. In this case the reaction proceeds in two steps, and the tertiary amine is produced by reaction of secondary amine first formed with the excess reagent, e.g.,



If a pure secondary phenylamine, unmixed with tertiary amine, is desired, it is possible to treat the sodium or potassium derivative of acetanilide with an alkyl halide:

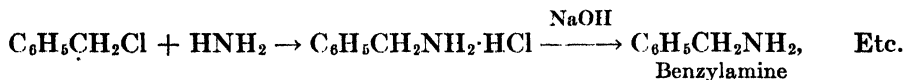


following this reaction with hydrolysis:



Another method involves the reduction of a Schiff base (page 468).

(4) Aryl derivatives of aliphatic amines are formed by methods which yield the aliphatic amines. Thus the action of ammonia or hexamethylenetetramine upon benzyl chloride produces benzylamine:

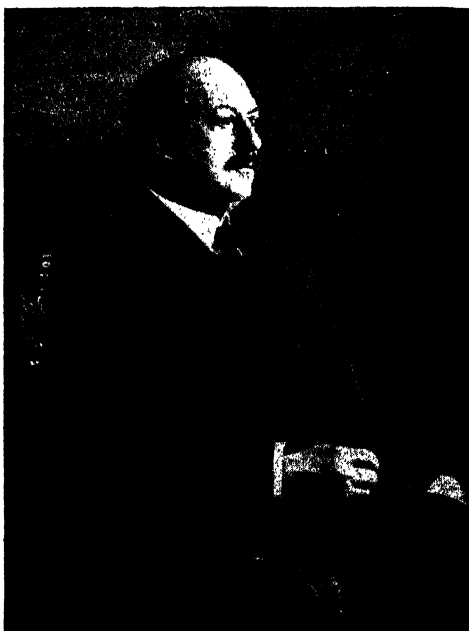
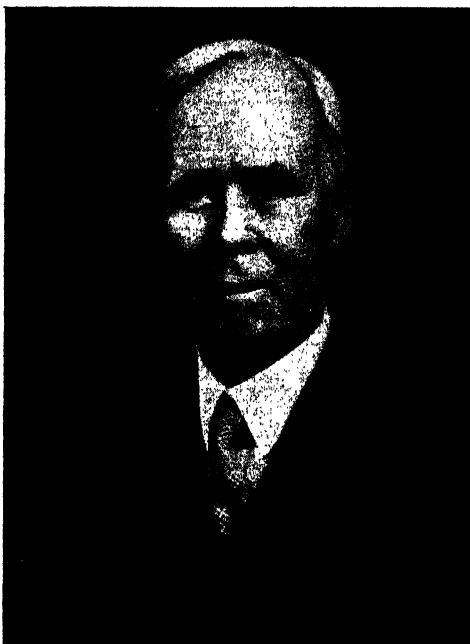


#### CHEMICAL REACTIONS OF AMINES

(The student should review the chemistry of the aliphatic amines before taking up this section.)

Many of the reactions of aromatic amines resemble those common to the aliphatic type. These will be mentioned first in this section, to be followed by examples of reactions in which the two classes are unlike in behavior.

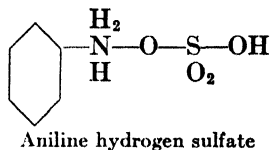
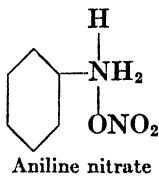
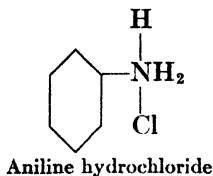
WILLIAM A. NOYES. (American. 1857-1941.) Noyes was for years the editor of the *Journal of the American Chemical Society* and active head of the chemistry department of the University of Illinois. His research includes atomic weight determinations, investigations of camphor, rearrangements, electron theory of valence. He was the author of influential texts in organic and general chemistry. See *J. Ind. Eng. Chem.*, **12**, 106 (1920).



LUDWIG GATTERMANN. (1860-1920, German.) Author of the well known laboratory text. Several syntheses bear his name (preparation of aromatic halogen compounds, aldehydes, hydroxy-aldehydes). He was associated with Victor Meyer at Göttingen and Heidelberg. See *J. Chem. Education*, **19**, 444 (1942); also this book, pages 483, 546.

*Berichte*, **54**, 115 (1921).

(1) *Salt formation.* Aromatic primary monamines readily form salts with acids. Those salts made from strong acids are stable substances. The nitrates and hydrochlorides are generally quite soluble in water, the sulfates somewhat less soluble.



Like ammonia and primary aliphatic amines, aniline forms a double-salt with platinic chloride:



The double-salts of aniline and the chlorides of tin are shown on page 459. Other such double-salts are known, but are less important than the above.

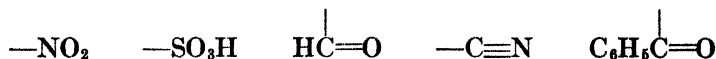
Salts of aniline are not neutral. Their water solutions are acid to litmus; likewise a solution of aniline in water is far less basic than ammonium hydroxide. Red litmus is not affected by such a solution, although it is sufficiently basic to precipitate ferric or aluminum hydroxides from their solutions.

The strength of the corresponding base is not greatly altered by substitution of alkyl groups either on the nitrogen or on the ring. Nitro groups on the ring lessen the basicity. An accumulation of aryl groups about the nitrogen of ammonia weakens its salt-forming powers. Thus diphenylamine forms salts only with the stronger acids, and these salts are completely hydrolyzed by water. Triphenylamine does not form salts with acids. As would be expected the diamines resemble monamines in their salt-forming powers. They are diacid bases (dibases).

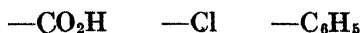
**Digression. Importance of Negative Groups.** This is a convenient point to summarize information about negative groups which has been given in previous chapters. By definition a negative group is one which, when introduced into a compound, reduces its basicity. Such a group when substituted into ammonia forms a compound which with water gives a base weaker than ammonium hydroxide. A negative group substituted for hydrogen of water yields a compound more acidic than water.

The typical negative groups are unsaturated at the point of attachment of the group, and usually contain one or more negative atoms.

Examples of strongly negative groups:



Examples of groups with smaller negativity:



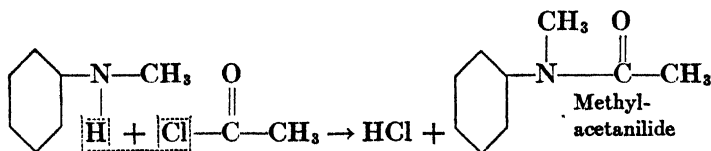
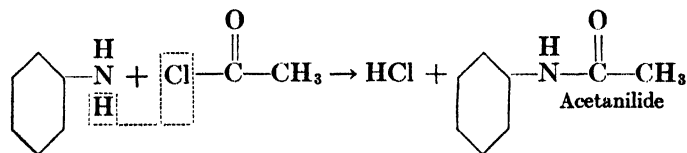
The following effects of these negative groups have been studied: (1) A negative group when substituted in the chain of an aliphatic acid increases the strength of the acid. This was laid to the power of the group to cause an electron drift towards itself and away from the carboxyl group (page 171). (2) The hydrogen of  $-\text{CH}_3$  and  $-\text{CH}_2$  group next to an unsaturated negative group is mobile. This is the cause of tautomerism of the keto-enol type, of which many instances have been shown; (3) examples of reduction of basicity by negative group have just been given in connection with di- and triphenylamine. The aliphatic and aromatic amides may be used as examples of compounds in which ammonia coupled with negative groups has lost its basic properties.

Chlorine atom properly belongs with negative groups because (a)  $\text{HOCl}$  is an acid; (b) although  $\text{Cl}$  is not a *meta*-directing atom on the benzene ring, it resembles the *m*-directing groups in its ability to hinder further substitution. Also the group  $-\text{CCl}_3$  is a *meta*-directing group. Such a group resembles  $-\text{NO}_2$  or  $-\text{SO}_3\text{H}$  in that there are many lone pairs of electrons.

(2) *Reactions with alkyl halides.* Aniline and its homologs react with alkyl halides. In this way salts of secondary and tertiary amines are formed (see page 462). The final product of such a reaction is a quaternary ammonium salt. Similar reactions of aliphatic amines are discussed on page 304. Secondary aryl amines react similarly with the alkyl halides, but tertiary aryl amines do not.

(3) *Reaction with active metals.* Hydrogen of the amino group of aniline may be replaced with an active metal, as with ammonia. The same reaction is shown by methylaniline and takes place readily with diphenylamine. Several syntheses with these salts have been shown.

(4) *Reactions with acyl halides.* Those aromatic amines in which hydrogen atom remains attached to nitrogen (primary and secondary types) are acted upon by acyl halides. Substituted amides called anilides (toluidides, etc.) are formed by this reaction:

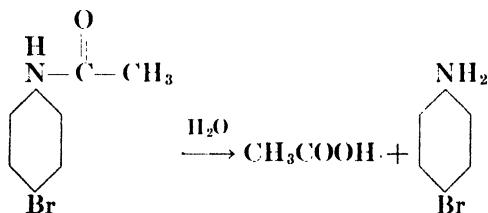


Anilides are also formed by the reaction of these amines with organic acids or their anhydrides.



The anilides in general are well crystallized substances with definite melting points. They are serviceable in the identification of specific amines. They are equally useful for the identification of organic acids. Also acetylation is frequently resorted to in preparing derivatives of aniline or its homologs, because the anilides are less reactive than the amines; moreover their reactions are more easily regulated.

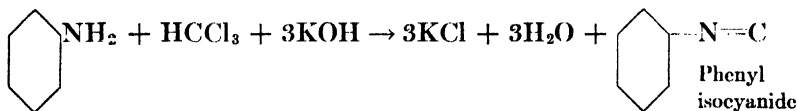
For example, *p*-bromoaniline cannot well be made by direct bromination of aniline; this gives tribromoaniline (page 471). However, bromination of acetanilide yields *p*-bromoacetanilide, which may then be hydrolyzed to acetic acid and *p*-bromoaniline:



An amino group treated in this way to decrease its activity during the course of a reaction is said to be "protected" or "blocked."

Acetanilide (antifebrin), which results from the action of acetic acid (acetic anhydride, acetyl chloride) and aniline, is used as a remedy for headache, neuralgia, mild fever. Methylacetanilide is also anti-neuralgic, but is more toxic than acetanilide.

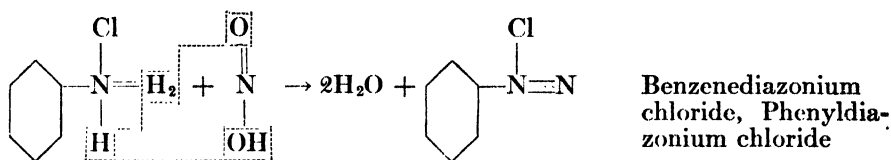
(5) *Reaction with chloroform and alcoholic potash.* The carbylamine reaction which is discussed on page 311 is common to the aromatic primary amines. Aniline by this treatment yields phenyl isocyanide:



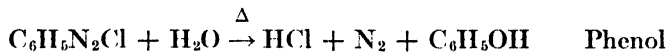
The reaction forms a test for aniline because of the powerful and unmistakable odor of the isocyanide.

(6) *Reactions with nitrous acid.* With the aromatic amines nitrous acid performs two offices. It enables us to distinguish the three types of amines one from another, in a manner analogous to that learned in the aliphatic series. Moreover, this reagent forms very important derivatives with the primary and mixed tertiary amines, the diazo and nitroso compounds respectively. These will be separately discussed in later paragraphs.

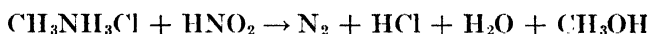
(a) Salts of primary amines like aniline, treated in the cold with nitrous acid, do not evolve nitrogen. Under such conditions a diazonium compound is formed.



The equation above shows diagrammatically what takes place, i.e., nitrogen of nitrous acid replaces the three hydrogen atoms of the amine salt. When heat is applied the diazonium salt is converted to a phenol:

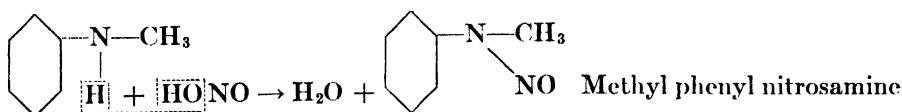


Thus a hydroxy-compound is formed from an amine by nitrous acid in the hot, exactly as with aliphatic amines:



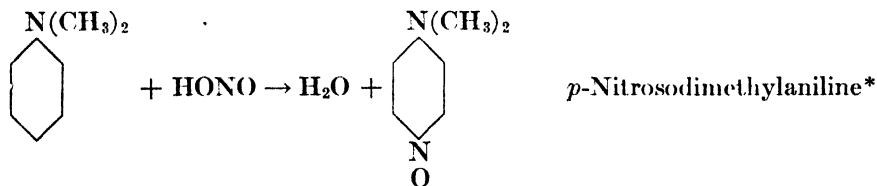
Aryl- and alkylamines differ in this respect, that the former allow the isolation of the intermediate diazonium compound (a valuable synthetic agent), while the latter liberate nitrogen at once and pass to alcohols.

(b) Secondary aromatic amines form nitroso compounds with nitrous acid:



This behavior is similar to that of aliphatic secondary amines.

(c) With the mixed tertiary arylamines the reaction with nitrous acid follows a new course. The NO group is linked not to nitrogen but to the *para* carbon of the ring. Thus nitrous acid with dimethylaniline yields *p*-nitrosodimethylaniline:

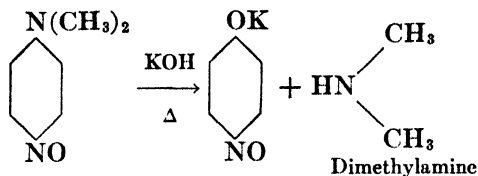


This unusual reaction makes it easy to distinguish tertiary aromatic amines both from other arylamines and from the tertiary aliphatic amines.

The hydrolysis of nitrosodimethylaniline and similar compounds is of interest, since it is a means of preparing pure secondary aliphatic amines.

\* In actual practice a salt is obtained, from which the free base shown is released by the action of alkali.

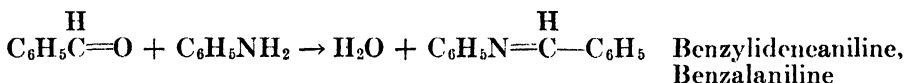
Example:



The nitroso group, like the nitro group, activates other groups *para* and *ortho* to it.

Nitrosodimethylaniline is a valuable intermediate for general synthetic uses. It is especially useful for dye preparation.

(7) *Reaction with aldehydes.* Aniline reacts in a complex manner with formaldehyde and other aliphatic aldehydes. Aromatic aldehydes condense to give compounds known as Schiff bases or anils.

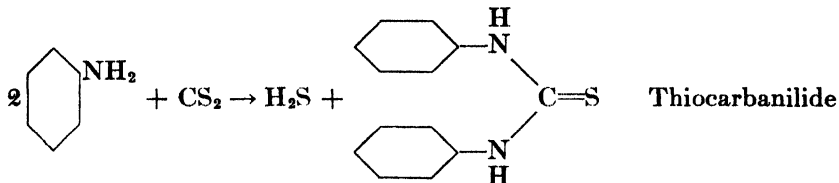


The reduction of the Schiff base gives a secondary amine,  $\text{C}_6\text{H}_5\text{N}(\text{H})\text{CH}_2\text{C}_6\text{H}_5$ . Schiff bases are useful synthetic compounds. Their formation is a means of blocking the amino group during a reaction (e.g., nitration). The Schiff bases are easily hydrolyzed by acids.

### REACTIONS OF ANILINE

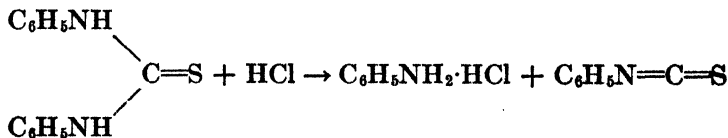
Several important reactions of aniline are as follows.

(1) *Reaction with carbon disulfide.* Aniline and other primary amines react with carbon disulfide to give derivatives of thiourca, with liberation of hydrogen sulfide. With aniline we get diphenylthiourea or thiocarbanilide:



The substance has importance as an accelerator in the vulcanization of rubber (in order to aid the reaction between rubber and sulfur in the vulcanization).

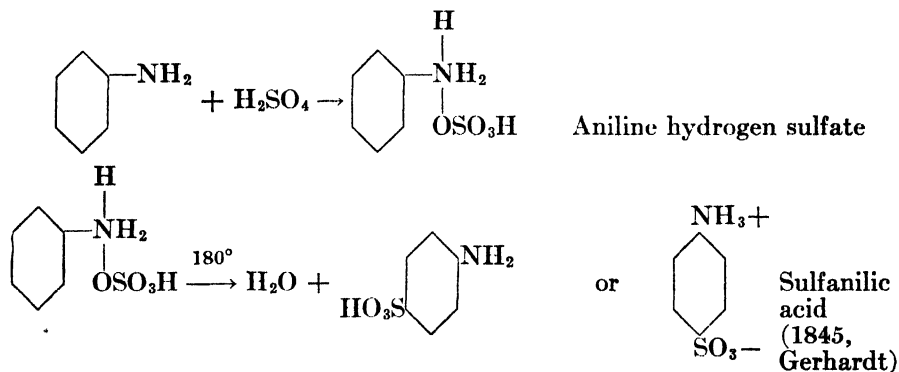
When heated with concentrated hydrochloric acid, thiocarbanilide forms phenyl isothiocyanate (phenyl mustard oil).



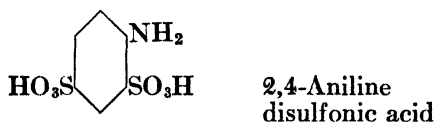
The isothiocyanates are called mustard oils after the allyl compound,  $\text{CH}_2=\text{CHCH}_2\text{N}=\text{C}=\text{S}$ , which is found in mustard seed (page 293). Phenyl mustard oil is used in synthetic work.

With phosgene, aniline gives phenyl isocyanate,  $\text{C}_6\text{H}_5\text{N}=\text{C}=\text{O}$ . This reagent is used to identify alcohols and primary and secondary amines through the formation of substituted ureas and urethans. (See page 290.) Naphthyl isocyanate is used in a similar way.

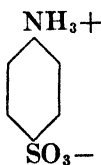
(2) *Reaction with sulfuric acid.* Aniline hydrogen sulfate is the first product formed in this reaction; on further heating this salt loses water and then undergoes rearrangement to *p*-sulfanilic acid:



Further sulfonation gives rise to aniline disulfonic acid:



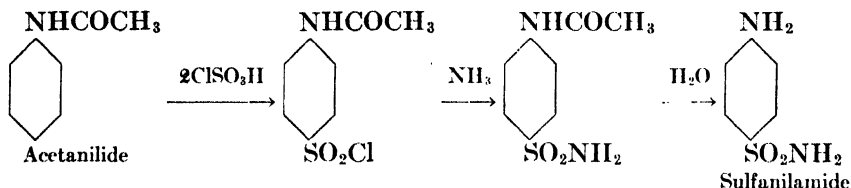
Sulfanilic acid is a solid, only slightly soluble in water or organic solvents. It has no definite melting point, but decomposes at about  $280^\circ$ ; in other words, it has certain resemblances to an inorganic compound. In sulfanilic acid the acid character of the sulfonic group overshadows the basic nature of  $\text{NH}_2$  to such an extent that the compound does not form salts with acids. The compound exists as an "internal salt" or zwitterion (see page 245).



Salts of sulfanilic acid (in which the sulfonic group is neutralized) act as bases; they behave like primary amines toward nitrous acid. Sulfanilic acid is important in the making of certain dyes.

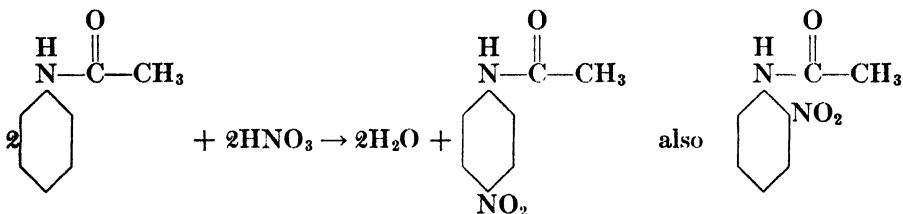
**Sulfa Drugs.** The amide of *p*-sulfanilic acid (sulfanilamide) is one of the new "sulfa" compounds whose use in medicine has effected a revolution in treatment of systemic bacterial infections. They are the only chemicals available which are effective in doses so small as to be harmless to the patient.

Sulfanilamide has been in use since 1933; it is used for streptococcal, meningococcal, and gonococcal infections. Sulfa drugs of later discovery are noted on page 647. Research in this field is very intense and the work promises further discoveries of equal importance to those already made. The synthesis of sulfanilamide is given herewith in outline form.

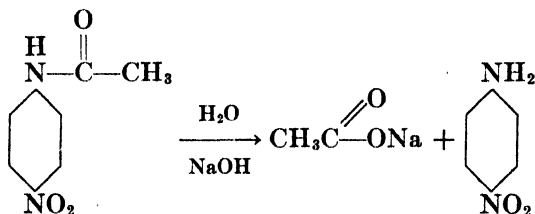


*p*-Arsanilic acid,  $\text{H}_2\text{NC}_6\text{H}_4\text{As}(\text{O})(\text{OH})_2$ , is made in the same way as sulfanilic acid, i.e., from aniline and arsenic acid. Its monosodium salt (Atoxyl) has been used in the treatment of sleeping sickness (p. 602).

(3) *Reaction with nitric acid.* When aniline is directly nitrated, oxidation takes precedence over nitration. However, when the amino group is "protected" by acetylation, nitration takes place in the *p*- and *o*- positions:



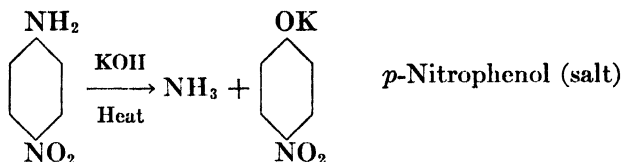
Hydrolysis of the resulting nitroacetanilides yields the *p*- and *o*-nitroanilines:



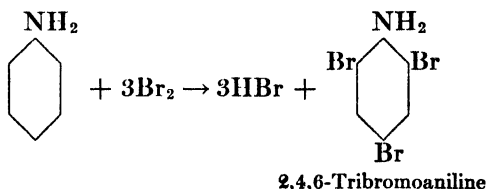
In this method the *para* compound predominates. By using acetic anhydride as a solvent, the yield of *ortho* compound is greatly increased (see page 444). *m*-Nitroaniline is made by the partial reduction of *m*-dinitro-

benzene (see page 449), or by nitrating aniline dissolved in concentrated sulfuric acid.

The  $\text{NH}_2$  group in *p*- or *o*-nitroaniline may be removed by treatment with alkali, its attachment to carbon being loosened by the presence of  $\text{NO}_2$  group:



(4) *Action of halogens.* Halogens act readily upon aniline even in water solution to form tri-substitution products. Bromine-water with aniline gives tribromoaniline:



The resulting tribromoaniline is insoluble in water and has a sharp melting point. It can therefore be used to identify the presence of aniline.

As already stated *p*-bromoaniline may be formed by the bromination of acetanilide, and hydrolysis of the resulting *p*-bromoacetanilide.

(5) *Oxidation of aniline.* When aniline is lightly oxidized with a mixture of sulfuric acid and potassium dichromate, a blue-black mixture called "aniline black" results. This is sometimes used as a stain (on desk-tops, etc.), also as a dye for cotton. Further oxidation yields the substance quinone (see page 560). When aniline is oxidized with a solution of bleaching-powder or sodium hypochlorite, a violet-colored solution is secured. This reaction (the "bleaching-powder test") may be used to test for small amounts of aniline.

#### REACTIONS WHICH IDENTIFY AMINES ✓

The following forms a summary and extension of the material already presented bearing on this subject.

##### (1) *Primary amines.*

- (a) React with acyl halides to form anilides.
- (b) Form derivatives with Hinsberg reagent, which are soluble in sodium hydroxide solution. (The Hinsberg reaction is explained on page 441.)
- (c) Undergo the carbylamine reaction.

- (d) Form derivatives of thiourea when treated with carbon disulfide.
- (e) Nitrous acid in the cold gives diazonium compounds.
- (f) In a hot solution nitrous acid yields free nitrogen and a phenol.

(2) *Secondary amines.*

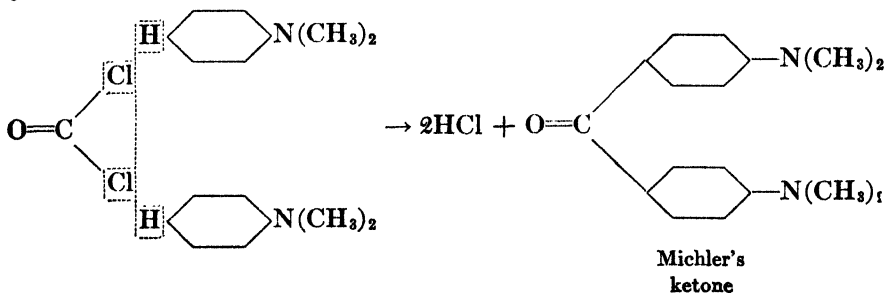
- (a) Form substituted anilides with acyl halides.
- (b) The Hinsberg reagent gives a product insoluble in sodium hydroxide solution.
- (c) Nitrous acid yields nitrosamines.

(3) *Tertiary amines.*

- (a) Do not react with acyl halides, or with Hinsberg reagent.
- (b) Aliphatic-aromatic type with nitrous acid give *p*-nitroso compounds.
- (c) With alkyl halides the mixed tertiary amines form quaternary ammonium salts.

**Michler's Ketone.** It has been noted that the *para* hydrogen atom of primary amines and of mixed secondary amines is quite active and easily replaced by substituting groups. The same is true of mixed tertiary amines of the type of dimethylaniline. (Note the reaction of this compound with nitrous acid, page 467.) Use is made of this fact in the preparation of derivatives of commercial importance. But one example will be given here, further examples being presented in the chapter devoted to dyes.

*Formation of Michler's Ketone, Tetramethyldiaminodiphenyl Ketone.* When dimethylaniline reacts with phosgene, the *para* hydrogen of two molecules of the former is removed as hydrogen chloride. In this way Michler's ketone is produced. The compound is used in making certain dyes.

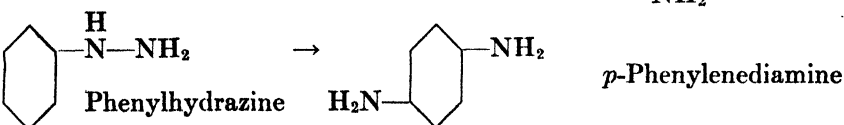
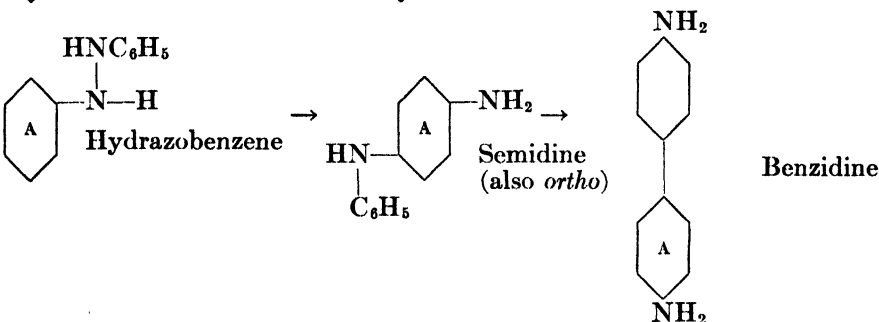
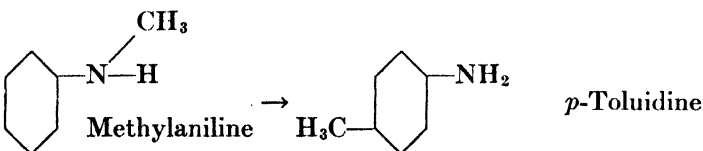
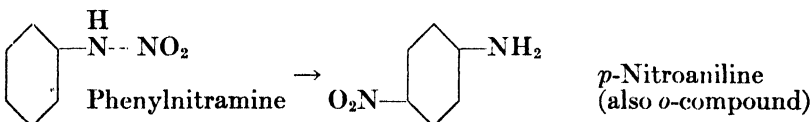
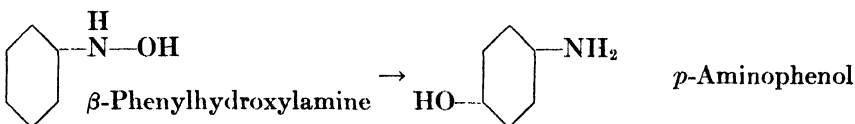
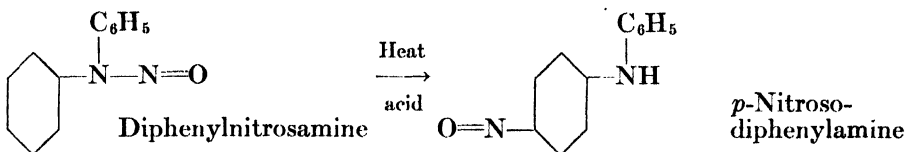


## REARRANGEMENTS OF SUBSTITUTED AMINES

Certain of the substituted anilines, when treated with strong acid under various experimental conditions, undergo a molecular rearrangement, one of the groups on the nitrogen atom changing place with the *para* hydrogen

of the ring. This reaction has already been noted in the change of methylaniline to *p*-toluidine and of aniline hydrogen sulfate to sulfanilic acid.

The new compounds formed by this rearrangement are usually more basic than before the shift, which explains the use of acid to promote the reaction. This same type of rearrangement may occur with the phenols and will be noted in the preparation of salicylic acid (page 500). The reaction is frequently quite useful in synthetic work. Some examples are given in the following equations, which show the substances before and after rearrangement.

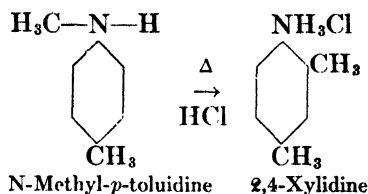


The examples above show *para* rearrangements and indicate cases in which the *ortho* compound is also formed. In certain instances the *ortho*



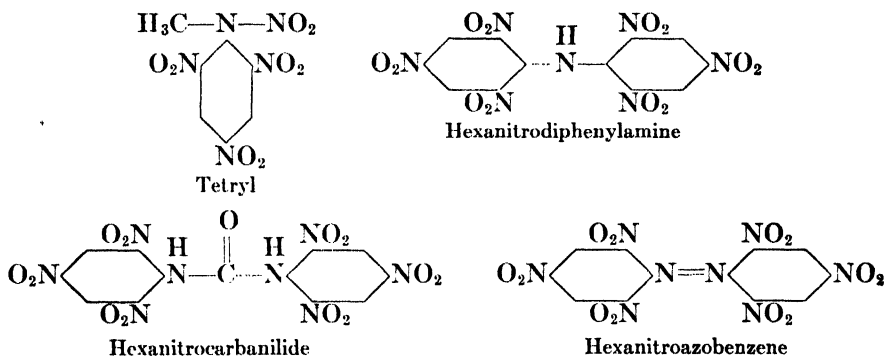


derivatives may be produced by this reaction when the *para* position in the ring is blocked. The following example shows the method used in the commercial production of 2,4-xylidine:



The rearrangement reaction discussed in this section does not yield *meta* derivatives.

**Explosives.** Tetryl (2,4,6-trinitrophenylmethylnitramine) is used in boosters. It is a more powerful explosive than T.N.T., also more sensitive to shock. The butyl analog (butyl tetryl) has uses similar to those of tetryl. Hexanitrodiphenylamine, hexanitrocarbanilide, hexanitroazobenzene, and 2,3,4,6-tetranitroaniline (T.N.A.), also have explosive properties.



For detailed descriptions of these compounds and their preparation, see Reference 8, page 478.

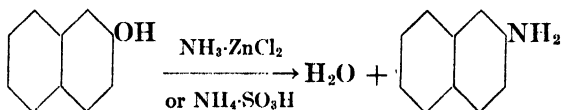
### BENZENEDIAMINES

The *orthodiamines* are of interest because of the many reactions by which they give ring closures. One of these, with phenanthrenequinone, is given on page 598. *Metadiazines* easily form dyes on diazotization, and also couple with other compounds to form dyes (page 679). *Paradiazines* are also useful in dye formation.

### AMINO DERIVATIVES OF NAPHTHALENE

Of the numerous amino compounds having complex nuclei, the naphthylamines are the most important.  $\alpha$ -Naphthylamine is formed by the reduction of  $\alpha$ -nitronaphthalene. It is a colorless solid, which upon exposure to air takes on a brownish color. The odor of the compound is dis-

agreeable.  $\beta$ -Naphthylamine may be formed by the action of ammonia upon  $\beta$ -naphthol:

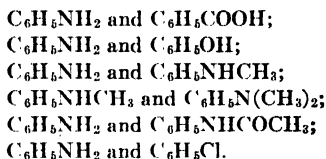


(See also page 516.) Both of these compounds are employed in making dyes. The *beta* compound is odorless.

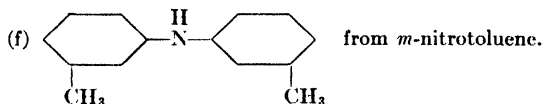
### REVIEW QUESTIONS

- Outline methods for the preparation of the following compounds from benzene: (a) *m*-Phenylenediamine; (b) Diphenylamine; (c) Triphenylamine; (d) Ethylaniline; (e) Diethylaniline.
- Illustrate by means of equations the reactions between aniline and: (a) Ethyl iodide; (b) Propionyl chloride; (c) Acetic anhydride.
- How may the following substances be made from aniline: (a) 2,4,6-Trichloroaniline? (b) *p*-Chloroaniline?
- Show by equations the reactions of nitrous acid with aniline, methylaniline, and dimethylaniline.
- How may diethylamine be made through the use of aniline?
- Outline the reactions by which phenyl isocyanide and phenyl isothiocyanate are made from aniline.
- Show by equations the methods used to form *p*-nitroaniline and *o*-nitrophenol from aniline.
- Give two methods of preparation of *p*-aminophenol.
- Discuss the use of the Hinsberg reagent in distinguishing primary, secondary, and tertiary amines from each other.
- Outline methods for the preparation of *o*-toluidine and *p*-toluidine from benzene.
- How could the following compounds be distinguished from each other: (a)  $\text{C}_6\text{H}_4\text{CH}_3(\text{NH}_2)$  and  $\text{C}_6\text{H}_5\text{NHCH}_3$ ? (b)  $\text{C}_6\text{H}_5\text{NH}_2\text{HCl}$  and  $\text{C}_6\text{H}_4\text{Cl}(\text{NH}_2)$ ?
- By the use of parallel equations show the points of chemical similarity and two points of difference between aniline and ethylamine.
- How could a mixture of aniline and nitrobenzene be separated?
- If 10 g. of aniline were made into the diazonium chloride, and this were then hydrolyzed, how much nitrogen gas would be produced?
- Show synthesis of aniline from the elements.
- Show and explain the formation of benzidine from nitrobenzene.
- Either acetyl chloride or acetic anhydride may be used to form acetanilide. Which gives the larger yield from a given weight of aniline?
- Show how to prepare *o*-, *m*-, and *p*-phenylenediamines from benzene.
- There are three diaminobenzoic acids which upon heating with soda lime give the same phenylenediamine. What is the structure of the latter and of the three acids?
- Compare the reaction of ammonium hydroxide with chlorobenzene and with 2,4-dinitrochlorobenzene.
- Give an example of the formation of an amino compound from a nitro compound by direct replacement of nitro group by amino group.
- Cite methods for protecting the amino group of aniline during reactions.
- When aniline is treated with phosgene it may form diphenylurea or phenyl isocyanate. What conditions would you use to get a good yield of the former compound?
- Outline the synthesis of *p*- and *o*-nitroanilines from chlorobenzene.

25. Why is *beta*-naphthylamine made from *beta*-naphthol instead of from the *beta*-nitro compound?
26. Cite several reactions which prove aniline to be more reactive than benzene.
27. If ammonia is heated with chlorobenzene to a high temperature to make aniline, what secondary organic product may appear?
28. Show the electronic structure of aniline hydrochloride (omit electrons of the ring).
- (R)29. Indicate how the following mixtures may be separated and the individual compounds made pure:



30. What compound would result upon heating each of the following compounds with hydrochloric acid? (a)  $\text{C}_6\text{H}_5\text{N}(\text{NO})\text{C}_2\text{H}_5$ ; (b)  $\text{C}_6\text{H}_5\text{NHNH}_2$ ; (c)  $\text{C}_6\text{H}_5\text{NHNHC}_6\text{H}_5$ .
31. Make a chart showing medical uses of suitable compounds mentioned in this chapter.
32. Cite three instances in which the chemistry of benzylamine differs from that of aniline.
33. Write sequences of equations showing how to make: (a) Benzylamine from benzene; (b)  $\alpha$ -Naphthylamine from naphthalene; (c) *m*-Nitroaniline from nitrobenzene; (d) *p*-Toluidine from toluene; (e) *p*-Chloroacetanilide from benzene;



34. Write graphic formulas of the compounds which would be formed by the reaction of: (a) Ethyl iodide and *N*-methylaniline; (b) Methyl bromide and *p*-ethylaniline; (c) Methyl iodide and *N*-ethylaniline.
35. Give equations for the preparation of sulfanilic acid. Give a short discussion of "sulfa" drugs.
36. Three compounds, (A), (B), and (C), have the same molecular formula. Analysis of (A) gave the following results: combustion of a 0.20 g. sample gave 0.582 g. of  $\text{CO}_2$ , and 0.1636 g. of  $\text{H}_2\text{O}$ . Another sample weighing 0.20 g. gave 21.38 cc. of nitrogen, measured over water at  $25^\circ\text{C}$ . The barometer read 742 mm. (vapor pressure of water at  $25^\circ\text{C}$ . = 23.8 mm.). (A) reacted with benzenesulfonyl chloride to give an alkali-soluble derivative; treatment of (A) with nitrous acid gave free nitrogen gas. The m.p. of (A) was  $-5^\circ\text{C}$ . Compound (B) when treated with benzenesulfonyl chloride gave a compound which was insoluble in alkali. Compound (C) did not react with benzenesulfonyl chloride. With nitrous acid it gave a derivative of m.p.,  $85^\circ\text{C}$ . which contained 18.67% of nitrogen. When the derivative was boiled with sodium hydroxide solution, a gas (b.p.,  $7.4^\circ\text{C}$ .) was liberated. A moist red litmus paper held in the gas was colored blue. The gaseous compound contained 31.11% of N. Prove the structures of (A), (B), and (C), writing equations for all reactions discussed.
37. Four aromatic nitrogen compounds have the same molecular formula based on the following percentages: C, 78.49%; H, 8.40%; N, 13.10%. Each gives a compound with hydrochloric acid containing 24.74% Cl. Compound #1 reacts with nitrous acid in the cold giving nitrogen gas and a new nitrogen-free compound. Compounds #2, #3, and #4 undergo a similar reaction when heated with nitrous acid. Suggest graphic formulas for the four compounds, and outline further experiments which will be needed to determine the structures.

38. An organic compound of molecular weight 108 contained 66.64% C, 7.41% H, and 25.93% N. When treated with hot solutions of sodium nitrite and hydrochloric acid it lost nitrogen gas and produced hydroquinone. Explain this reaction and deduce the structure of the original compound.

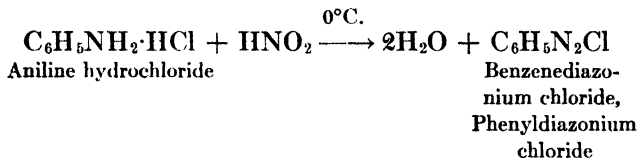
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## DIAZO COMPOUNDS AND DERIVATIVES

Sufficient evidence was presented in the last chapter to indicate the strategic position of aniline and the other primary amines in aromatic synthesis. However a number of the derivatives shown were substitution products in which the amino group remained intact, and these substances therefore maintained to some extent at least, the character of primary amines. We are now to consider derivatives of aniline and aniline homologs in which the amino group is replaced, or radically altered, through the intermediate formation of a diazo or a diazonium compound.

**Diazotization.** The reaction called *diazotization* takes place when a salt of a primary aromatic amine is treated with nitrous acid. Ordinarily, the salt is dissolved or suspended in water, and enough acid is added to form nitrous acid from sodium nitrite, a solution of which is poured into the acidified amine; the ratio of acid to amine is about 2.5 equivalents to one.



An amino compound so treated is said to be *diazotized*. As long as the solution is kept cold, no nitrogen is liberated (see page 311).

It is impossible to isolate the diazonium salt by the evaporation of such a solution, since hot water causes its decomposition in the sense of the following equation:



However, if the amine dissolved in absolute alcohol is treated with sufficient acid and either amyl or ethyl nitrite,\* the diazonium salt precipitates from the solution. Full precipitation is secured by the addition of ether.

Diazonium salts have been isolated in this manner. The dry salts are quite unstable and are apt to be explosive.† However, their water solutions serve all the needs of synthetic work.

In laboratory work the salts are seldom isolated in a pure state, and then only in minute amounts, on account of their dangerous character. In dye

\* The acid and ester react to produce nitrous acid.

† These salts have been proposed for use as explosives and several have been used as detonating agents.

making it is desirable to have stable diazonium salts on hand to avoid the necessity of making them on the spot. Diazonium salts developed to meet this need will be described later. In laboratory work a diazonium salt solution is commonly used at once. Upon standing, especially when exposed to light, the dissolved salts decompose. Negative groups on the ring decrease the stability to light; however in all cases exposure to strong light should be avoided.

### STRUCTURE OF DIAZONIUM SALTS

The diazonium salts and their solutions show many analogies in their reactions and properties to those of the quaternary ammonium salts. Thus:

(1) Solutions of diazonium salts of strong acids are neutral; electrical measurements show that the salts are highly ionized in dilute solutions.

(2) When a solution of benzenediazonium chloride is treated with silver hydroxide, a precipitate of silver chloride results, the solution at the same time becoming strongly basic. Its properties suggest those of such strong ammonium bases as tetramethylammonium hydroxide (page 309).



Various diazonium salts such as the nitrate, sulfate, or chloride may be obtained from the solution of benzenediazonium hydroxide by appropriate treatment with acids. The hydroxide itself has never been isolated.

As all ammonium bases contain "pentavalent" nitrogen, the structure of benzenediazonium hydroxide is made to conform to the general rule; the name-ending "onium" suggests this structure. The structure of benzenediazonium chloride is then as follows:

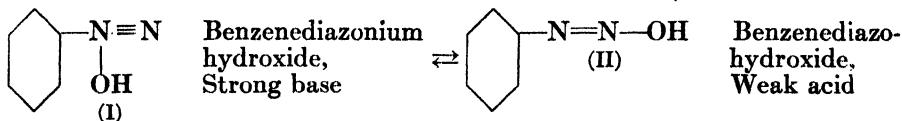


Other diazonium salts are presumed to have similar structures. In these formulas one of the nitrogen atoms is "pentavalent" as in ammonium salts; the other is trivalent. The name diazonium (Azote, French = nitrogen) indicates that two nitrogens are attached to one benzene ring, in other words the  $\text{N}:\text{N}(\text{OH})$  group is monovalent. This is borne out by the fact that this group may be replaced by monovalent units like OH, Br, I, OEt, etc., as we shall find, but not in any case by a divalent group.

### DIAZO SALTS

A solution of benzenediazonium hydroxide on treatment with an alkali base becomes less and less basic, finally showing the properties of a weak acid, forming a salt (diazotate) with the alkali base. This change of prop-

erty is believed to result from a shift or rearrangement of the molecule by means of which the "pentavalent" nitrogen becomes trivalent:

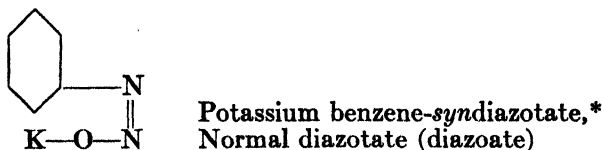


Various derivatives formed from alkaline solutions of diazonium salts are found to have their nitrogen atoms joined each to each as in the above suggested formula for benzenediazohydroxide. Examples of these compounds are aminoazobenzene and hydroxyazobenzene (page 485). Other examples of such compounds will appear in later discussion. Thus, aside from the fact that the structure presented for benzenediazonium hydroxide does not represent the reaction observed in an alkaline medium, there is additional evidence for structure (II) above in the known structures of the derivatives. The name *diazonium* is reserved for the derivatives of type (I), while those of type (II) are called *azo* or *diazo* compounds according to whether they have structure  $\text{Ar}-\text{N}=\text{N}-\text{Ar}$  or  $\text{Ar}-\text{N}=\text{N}-$ . Ordinarily the name diazo compound is rather loosely applied to any compound made by diazotization.

**Structure of Diazotates.** In fixing the structure of diazo compounds, a new difficulty arises in that the salts of benzenediazohydroxide (diazotates) have two forms. These differ from each other in several ways, notably in the greater ability of one of the salts to form dyes when treated with amines or phenols.

To repeat: when a saturated solution of benzenediazonium chloride is treated with an excess of concentrated potassium hydroxide, potassium benzenediazotate is formed. This salt in alkaline solution forms dyes with various aromatic phenols and amines. If a solution of potassium benzene-diazotate is digested with concentrated KOH for a short time at 130–135°, the salt secured is less reactive in dye formation (this power may be entirely lost in similar treatment of other like compounds.)

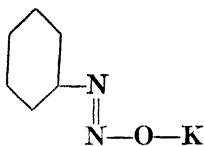
According to Hantzsch, the two diazotates are geometrical isomers, examples of isomerism of the *cis-trans* type which is discussed on pages 59 and 328. The more active salt which is first formed when a benzene-diazonium salt is treated with a base is assigned the *syn* (*cis*) structure:



\* Salts like these have been called diazotates; the term diazoate was recommended by the I.U.C. (see page 36).

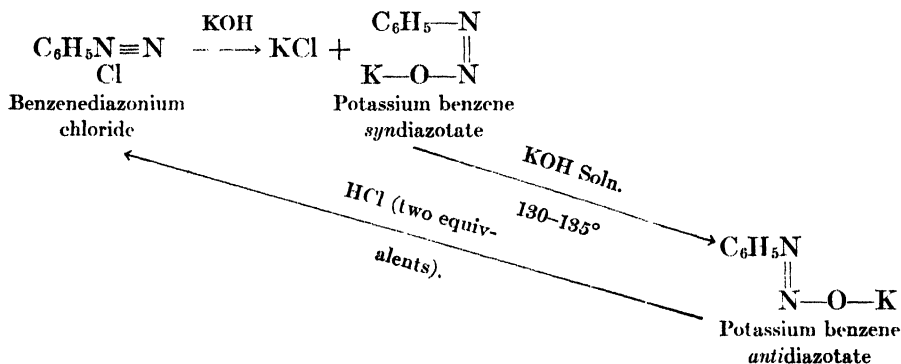


It is unstable and tends to pass into the *anti* (*trans*) form:



Potassium benzene-*antidiazotate*,  
Isodiazotate (isodiazoate)

which is less reactive and does not readily form dyes. Although the *syn*-potassium benzenediazotate changes in a hot strongly alkaline solution to the *anti*-diazotate, the reverse change does not readily take place. Ordinarily to make the *syn* compound from the *anti*, this is transformed to a diazonium salt by the addition of acid, and again treated with a base. The changes discussed in the preceding paragraphs are summarized in the following scheme:\*



### REACTIONS OF DIAZONIUM SALTS

**Replacement Reactions.** Diazonium salts undergo a number of transformations, by means of which the characteristic  $-\text{N}\equiv\text{N}$  group ( $\text{X} = \text{an}$

acid radical) is replaced by other monovalent groups or atoms. The most important of these changes are:

(1) *Replacement by hydrogen; formation of a hydrocarbon.* Under certain conditions of temperature, pressure, etc., ethyl alcohol reduces benzenediazonium salts to the corresponding hydrocarbons, being itself oxidized to acetaldehyde:



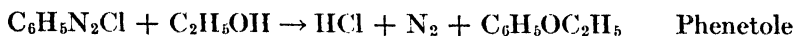
Formic acid or alkaline stannous chloride solution (sodium stannite) may

\* Though it is agreed that the isomerism of the diazotates is of the geometrical type, the evidence for the structures (*syn*, *anti*) given here is not sufficient to guarantee their correctness. That is, the first diazotate formed may be the *anti*, not the *syn*, and vice versa. Though the structures of diazonium salts and diazotates have been investigated for seventy years and by the ablest of chemists, uncertainty yet remains.

also be used to perform the reduction. Alkaline formaldehyde solution is useful in many cases.

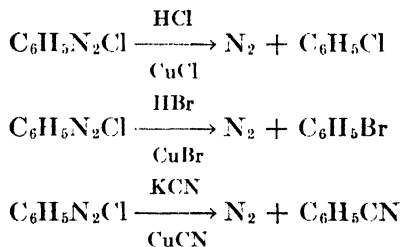
(2) *Replacement by hydroxyl; formation of a phenol.* An aqueous solution of a diazonium salt loses nitrogen when heated. A phenol results from this reaction. (See equation, page 479.) The solution should be strongly acid.

(3) *Replacement by alkoxy\* group; formation of a mixed ether.* Under proper temperature and pressure conditions, alcohols react with diazonium salts to form mixed ethers (aliphatic-aromatic) of the type of phenetole:



This reaction usually takes precedence over (1) shown above. However, the presence of negative groups on the ring favors reduction. A negative group in *ortho* position has maximum effect.

(4) *Replacement by a halogen or CN group; formation of an aryl halide or nitrile.* The following three reactions are known as **Sandmeyer reactions**.



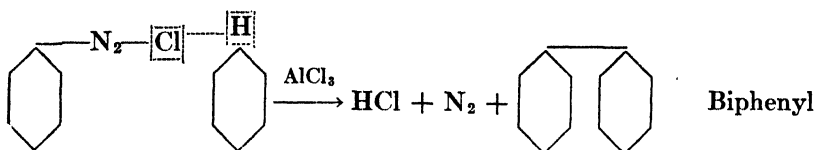
To bring about this kind of replacement, the diazonium salt solution is treated with the corresponding cuprous salt and halogen acid, and heated to drive off nitrogen. In making the cyanides, potassium cyanide is added to the cuprous salt in lieu of hydrogen cyanide.

Iodobenzene may be made without the use of the cuprous salt; in this case potassium iodide is employed. Also, the Cl, Br, and CN groups may be introduced by using fine copper powder with the proper potassium salts (**Gattermann reaction**).

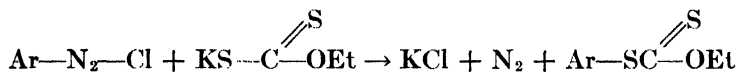
Fluoro compounds are made by adding fluoboric acid to the diazonium salt solution. This precipitates the aromatic borofluoride  $[\text{ArN}_2]\text{BF}_4$  which when heated yields boron fluoride, nitrogen, and the desired fluorine derivative.

(5) *Replacement by a hydrocarbon group.* A dry diazonium salt will react with an aromatic hydrocarbon to form a complex hydrocarbon, with elimination of nitrogen. The reaction is aided by the presence of aluminum chloride. The reaction can also be carried out in alkaline solution, which may be more convenient and safer. Cuprous oxide may be used as catalyst. The reaction is frequently used for closing rings.

\* An alkyl radical joined to oxygen is called an alkoxy group (see page 104).



(6) *Replacement by SH or SR.* Reaction of a xanthate with a diazonium salt gives an aryl substitution product of xanthic acid:



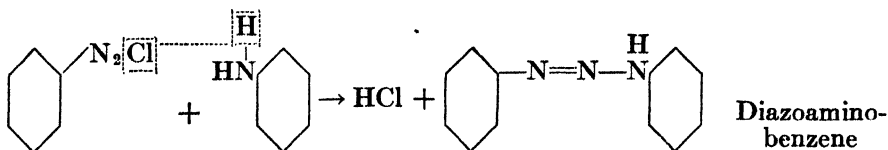
which upon heating yields  $\text{Ar-S-Et}$ , and upon hydrolysis gives  $\text{Ar-SH}$ .

(7) *Replacement by nitro group.* Since the amino group is usually obtained from the nitro group this replacement seems useless, but it must be remembered that the amino group can be formed otherwise, for example from hydroxyl. The sequence would then be:  $\text{ROH} \rightarrow \text{RNH}_2 \rightarrow \text{RN}_2\text{Cl} \rightarrow \text{RNO}_2$ . The diazonium salt solution is treated with excess nitrous acid and cuprous oxide.

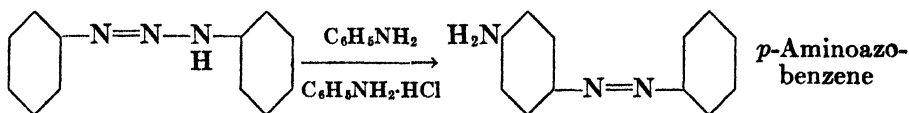
#### FURTHER REACTIONS OF DIAZONIUM SALTS

Several of the reactions observed with diazonium salts do not involve the loss of nitrogen atoms from the molecule. Derivatives formed in these reactions have the following nitrogen linkage:  $\text{X-N=N-Y}$ . Among the reactions in which *nitrogen is undisturbed* are:

(1) *Reaction of a diazonium salt and a primary amine in a neutral or faintly acid solution; formation of a diazoamino compound.* An example of this type of reaction is that of benzenediazonium chloride and aniline whereby diazoaminobenzene is formed:



Diazoaminobenzene is a rather unstable compound, melting at  $96^\circ$  but exploding at higher temperatures. Its most important reaction is its transformation to *p*-aminoazobenzene when heated with aniline and aniline hydrochloride:

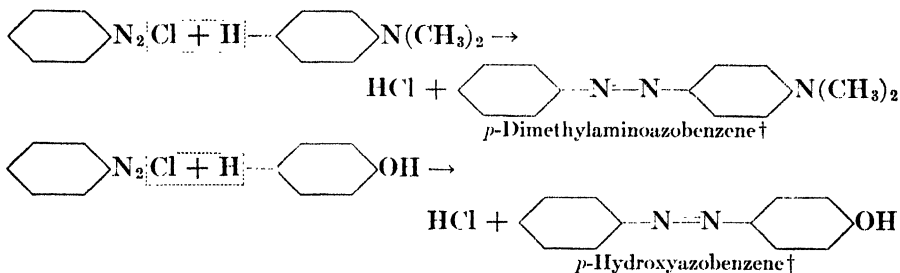


Aminoazobenzene salts are dyes (yellow) though unimportant as such, the chief use of the compound being for the production of its derivatives, which

have superior value as dyes. Another synthesis of aminoazobenzene is indicated in the following paragraph.

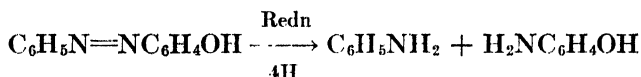
(2) *Formation of an azo dye by "Coupling" reaction in alkaline solution.* It was previously thought that the coupling was accomplished by the *syn* form of the diazo compound; the view now being advanced is that the coupling is through the agency of the diazonium ion. Coupling occurs both with amines\* and with phenols, attacking in each case the *para* position of the ring. If this position is occupied, *ortho* derivatives may result. *Meta* coupling does not occur.

Examples:

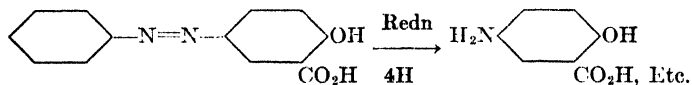


Coupling may take place with phenolic ethers if an active diazo compound is used, also in certain cases with benzene itself. The rate of the coupling reaction is increased by negative groups (Cl, NO<sub>2</sub>, SO<sub>3</sub>H) substituted in the ring of the diazonium salt.

When an azo dye is formed, two rings are associated with the nitrogens, ArN=NAr. Confirmation of this structure is afforded when such substances are reduced. In this reaction, amines are formed, the two nitrogens being separated:



This reaction is sometimes useful for the introduction of amino group. Thus aniline may be diazotized and coupled with salicylic acid. Upon reduction the intermediate compound gives aminosalicic acid and aniline:



The name *diazo* is dropped in favor of *azo* for such compounds to indicate that they have aryl group attached to each nitrogen.

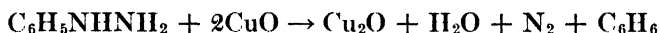
\* With a primary or secondary amine a diazoamino compound may be intermediate.

† These compounds are not effective dyes but are used to illustrate the reaction because they have simple structures.

(3) *Partial reduction of a diazonium salt; formation of a hydrazine derivative.*

**Phenylhydrazine.** This compound is prepared from benzenediazonium chloride by reduction in acid solution with stannous chloride, or by the use of sodium sulfite solution to yield, finally, phenylhydrazine hydrochloride,  $\text{C}_6\text{H}_5\text{NHNH}_2 \cdot \text{HCl}$ , from which the free base is easily obtained. Phenylhydrazine is a liquid (m.p.,  $19.6^\circ$ , b.p.,  $243.5^\circ$ ) of an unpleasant odor, suggestive of aniline. Exposed to light and air it rapidly darkens to a cherry-red color. It is somewhat toxic and should be handled with care.

The compound when boiled with alkaline copper sulfate (Fehling's solution), or ferric chloride, loses nitrogen:

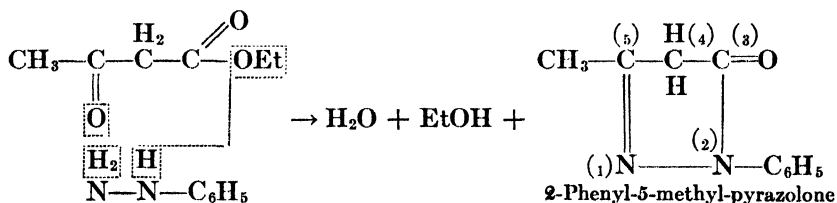


This reaction allows us to change nitrobenzene, aniline, etc., to benzene. Upon reduction, phenylhydrazine is transformed to aniline and ammonia, the two nitrogens parting company. Moderate oxidation of phenylhydrazine hydrochloride with mercuric oxide yields benzenediazonium chloride.

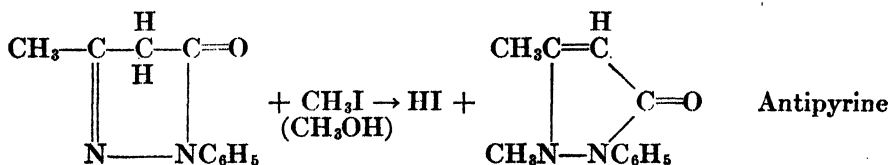
Phenylhydrazine is extremely useful in characterizing aldehydes and ketones, with which it forms the solid phenylhydrazones. In the chemistry of the carbohydrates it occupies a unique position, enabling one to change aldoses to ketoses.

**Antipyrine**, an important remedy for headache and neuralgia, a sedative and febrifuge, is a phenylhydrazine derivative. The steps in its synthesis are shown below.

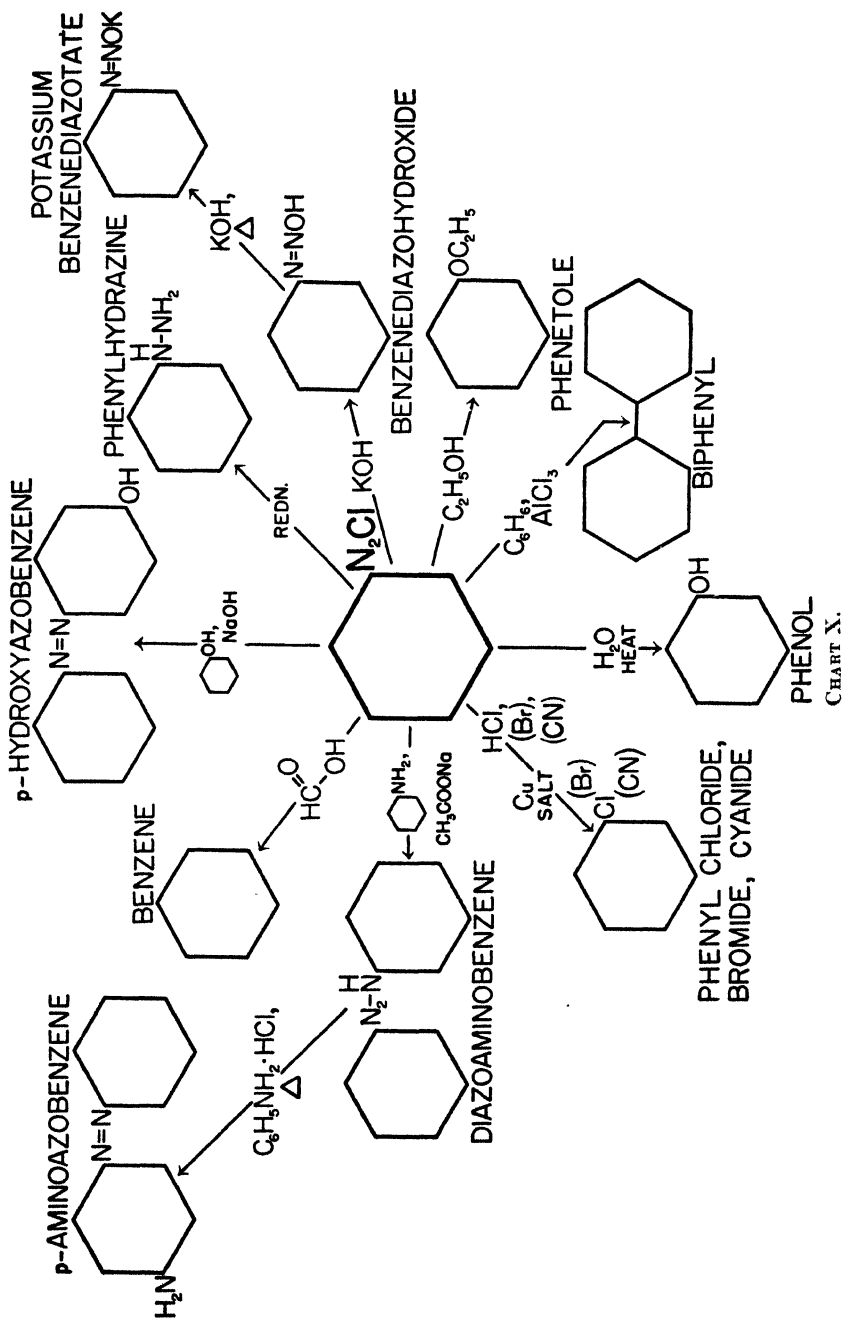
(a) The reaction of phenylhydrazine and acetoacetic ester, with the loss of a molecule each of water and of alcohol, yields phenylmethylpyrazolone:



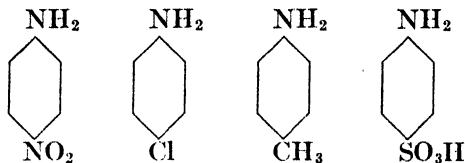
(b) The compound so formed is a derivative of the pyrazolone nucleus. Antipyrine results when phenylmethylpyrazolone is treated with methyl iodide in methyl alcohol:



SCHEME OF REACTIONS OF DIAZO COMPOUNDS



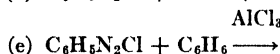
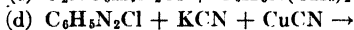
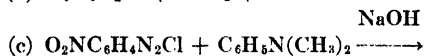
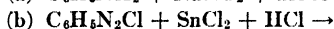
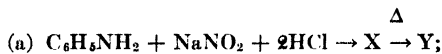
**Scope of Diazo Reaction.** For reasons of simplicity, all of the reactions of diazonium salts so far discussed in this chapter have been applied to benzenediazonium chloride. It must, however, be clearly understood that all primary aromatic monamines may be diazotized and subsequently carried through the transformations which have been illustrated. Also substituted amines such as the following:



may be employed, as well as amino derivatives of some ring compounds other than benzene. The reaction of diazotization thus becomes one of the most useful of the synthetic methods of aromatic organic chemistry.

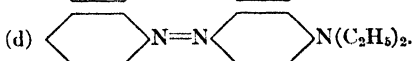
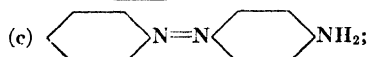
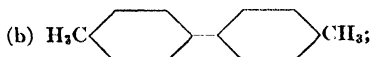
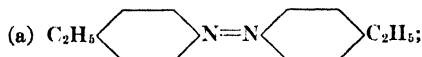
### REVIEW QUESTIONS

1. What is the evidence for the ammonium structure assigned to benzenediazonium salts?
2. Discuss the structure assigned to the diazotates.
3. How may the following compounds be made from aniline: (a) Phenol? (b) Benzene? (c) Anisole? (d) Phenyl cyanide? (e) Biphenyl? (f) *p*-Aminoazobenzene?
4. Write equations for the formation of the following from aniline: (a) Phenylhydrazine; (b) Antipyrine; (c) *p*-Ethylphenol.
5. Complete the following equations.

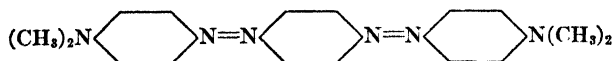


6. Specify the necessary conditions and the amounts of chemicals needed for the diazotization of 25 g. of aniline; of 15 g. of *p*-toluidine.
7. How may phenylhydrazine be converted to: (a) Phenol? (b) Phenyl chloride?
8. Write equations for the conversion of *p*-nitroaniline to *p*-chloronitrobenzene.
9. How may the arrangement of nitrogen atoms in an azo compound be confirmed?
10. How many cc. of nitrogen would result from the treatment of 10 g. of phenylhydrazine with an excess of Fehling's Solution. How much cuprous oxide would be formed?
11. Name five derivatives of aniline prepared through different applications of the diazo reaction, and give a use for each.
12. Show by sequences of equations how to make the following compounds from aniline: (a) *p*-Dichlorobenzene; (b) 1,3,5-Trichlorobenzene; (c) *p*-Diethylaminotoluene; (d) *p*-Methoxytoluene; (e) *p*-Carboxytoluene.
13. Show by sequences of equations how to make the following compounds from benzene: (a) 1-Amino-3-methyl-4-bromobenzene; (b) *m*-Dicarboxybenzene; (c) *p,p'*-Dimethylbiphenyl; (d) *p*-(Methylamino)chlorobenzene.

14. Indicate how the following compounds may be synthesized from toluene: (a) *p*-Tolylhydrazine; (b) Di-*p*-tolyl ether; (c) *p*-Cresol; (d) *p*-Chlorotoluene.
15. Using only aniline and ethyl bromide as organic source materials, synthesize *p*-bromoaniline. Both source materials must be used.
16. How would you make *o*-iodoaniline from *o*-nitroaniline?
17. If a water solution of benzenediazonium chloride shows the presence of chloride ion and is neutral, what do we know regarding the strength of the base benzenediazonium hydroxide?
18. If a diazonium salt solution is to be heated to form a phenol it should be strongly acid. Why? A solution of a diazonium nitrate would not be very suitable for this reaction. Why?
19. When diazotization is carried out too rapidly some amines give nitroso compounds. Explain how this could occur. Give another valid reason for avoiding an excess of nitrous acid during a diazotization.
20. If during the diazotization of aniline an excess of sodium acetate is added to the solution, diazoaminobenzene precipitates. Explain its formation. Devise another method for making diazoaminobenzene.
21. Write full equations for the following syntheses from benzene: (a) *m*-Dibromobenzene; (b) *p*-Tolylhydrazine; (c) *n*-Butyl phenyl ether.
- (R)22. The reduction of methyl-phenyl-nitrosamine gives methylphenylhydrazine; the same compound is formed when methyl bromide acts upon the *alpha* monosodium derivative of phenylhydrazine. Show how these facts establish the structure of phenylhydrazine.
23. Explain by the use of equations how the following compounds may be converted to benzene.
- (a)  $\text{C}_6\text{H}_5\text{COOH}$ ; (b)  $\text{CH}_3\text{C}_6\text{H}_4\text{COOH}$ ; (c)  $\text{O}_2\text{NC}_6\text{H}_4\text{NO}_2$ ; (d)  $\text{O}_2\text{N}^+\text{C}_6\text{H}_4\text{NHNH}_2$ ; (e)  $\text{HOC}_6\text{H}_4\text{NH}_2$ .
- (R)24. Show how to make the following compounds from *p*-nitrotoluene. (a) *m*-Bromochlorobenzene; (b) *m*-Phenylenediamine; (c) *o*-Toluic acid.
25. Outline the synthesis of each of the following from benzene.



26. Tell how to make the compound with this formula:



- (R)27. Discuss the following reactions, writing an equation for each. Benzene is nitrated at  $60^\circ\text{C}$ . with concentrated nitric and sulfuric acids. The product is reduced with tin and hydrochloric acid. After isolation of the new compound this is treated with one mol of sodium nitrite and excess of hydrochloric acid. The resulting solution is added to an alkaline solution of  $\beta$ -naphthol.
28. Discuss the isomerism of the diazotates.



29. Write a complete scheme for the preparation of antipyrine. Any inorganic compounds may be used, but all organic materials must be made either from methyl or ethyl alcohol.

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2. SAUNDERS. *The Aromatic Diazo Compounds and their Technical Applications*. (Arnold, 1937.)
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4. GROGGINS. *Unit Processes in Organic Synthesis*. McGraw-Hill Book Co., 1938, 115. (Diazotization.)
5. WISTAR and BARTLETT. Kinetics and mechanism of the coupling of diazonium salts with aromatic amines in buffer solutions. *J. Am. Chem. Soc.*, **63**, 413 (1941).
6. HAUSER and BRESLOW. Condensations. XV. The electronic mechanism of the diazo coupling reaction. *J. Am. Chem. Soc.*, **63**, 418 (1941).
7. GOMBERG and BACHMANN. The synthesis of biaryl compounds by means of the diazo reaction. *J. Am. Chem. Soc.*, **46**, 2339 (1924).

## CHAPTER XXVI

### AROMATIC ALCOHOLS, PHENOLS

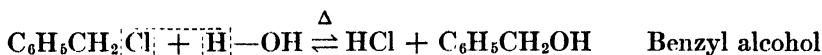
Two distinct types of hydroxy compounds are possible in the aromatic series, corresponding to the attachment of the OH group directly to the ring or to an alkyl side-chain. Compounds of the former class are known as *phenols* if the benzene ring is involved. The corresponding compounds of naphthalene are the *naphthols*. They will be described on subsequent pages. The differences between the two types of aromatic hydroxy compounds will be emphasized during the discussion of the phenols. For the present, suffice it to say that those aromatic compounds which have OH group substituted in the side-chain are true alcohols. In reactions, mode of preparation, and in some of their physical properties they are closely akin to the aliphatic alcohols.

#### ALCOHOLS

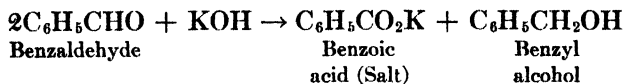
The simplest representative of the aromatic primary alcohols is benzyl alcohol,  $C_6H_5CH_2OH$  ( $C_6H_5CH_2$  is the benzyl radical). This substance, which is an oil, boiling at  $204.7^\circ$ , is found in nature in the form of an ester in balsam of Peru and of Tolu, and in the oils of a number of flowers. It is used to prepare perfumes, also as a local anesthetic. Ephedrine (page 742) is an important derivative.

**Preparation.** Benzyl alcohol may be made by methods already familiar for the preparation of aliphatic alcohols, i.e.,

(1) By hydrolysis of the corresponding halogen compounds. Benzyl chloride heated with water, or better, with a solution of potassium carbonate yields benzyl alcohol:



(2) Aromatic aldehydes, when treated with a strong base, undergo mutual oxidation and reduction between the molecules, half of the substance being oxidized to the corresponding acid, while half is reduced to the alcohol stage. (Cannizzaro reaction.) By this method benzyl alcohol is prepared from benzaldehyde:

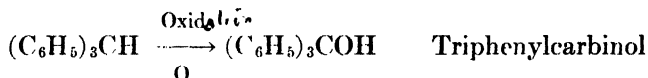


Formaldehyde has been cited as an example of an aliphatic aldehyde which

follows this type of reaction. Other aliphatic aldehydes possessed of *alpha* hydrogen atoms give resins when acted upon by a strong base. Those which have no *alpha* hydrogen (trimethylacetaldehyde for example) do not form resins.

The methods cited for the preparation of benzyl alcohol will answer for any of the primary aromatic alcohols. Alcohols of the *secondary* type are, like aliphatic secondary alcohols, the reduction products of the corresponding ketones. Also they may be prepared through the use of the Grignard reaction, as described in Chapter XXIX.

*Tertiary* aromatic alcohols result from the Grignard reaction, again they are formed by the oxidation of an aromatic hydrocarbon:

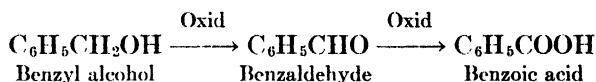


The heavy loading of the tertiary carbon atom makes oxidation easy. Similar activity of tertiary carbon atom and of carbon atom with heavy load has been noted before (pages 32, 116).

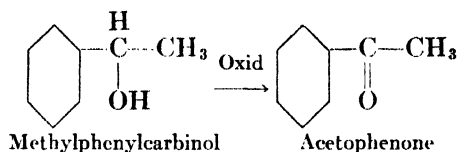
#### REACTIONS OF AROMATIC ALCOHOLS

The reactions are those already learned from study of the aliphatic alcohols. A few examples will illustrate this likeness.

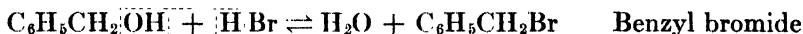
(1) *Oxidation.* Primary alcohols oxidize first to aldehyde, then to acid:



Secondary alcohols oxidize to ketones:

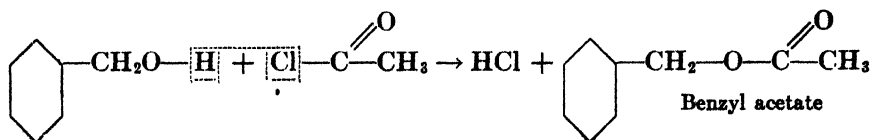


(2) *Action of halogen acid; formation of a halide.*



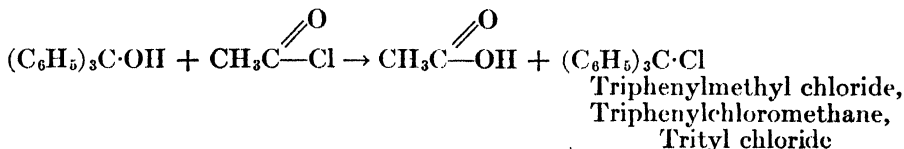
As explained in the next paragraph, this action proceeds more readily than with aliphatic alcohols.

(3) *Action of organic acid (anhydride, acid chloride); formation of an ester.*

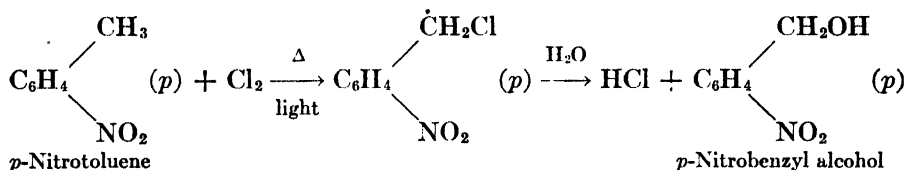


Benzyl acetate has the odor of jasmine. It is used in artificial perfumes and as a solvent for airplane dopes. Benzyl benzoate,  $C_6H_5COOCH_2C_6H_5$ , is used in perfumes, and in remedies for asthma and whooping cough.

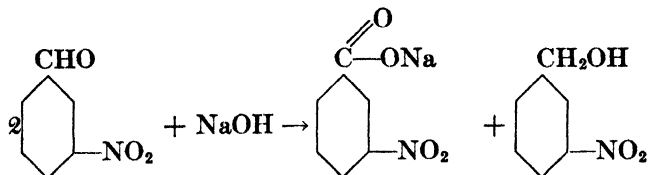
The OH group of the aromatic alcohols is not held so firmly to carbon as in the aliphatic alcohols. This is especially the case when the group is *alpha* to the ring. Thus the formation of a halide by action of a halogen acid (see (2) p. 492), proceeds at a lower temperature. In the case of the tertiary alcohols the activity of the OH group is such that a *chloride* and not an ester is formed by the action of an acid chloride:



The negative phenyl group is responsible for this activation. This activity often renders necessary the employment of indirect methods for the introduction of other groups into the ring; for instance, nitrobenzyl alcohol could not be prepared by direct nitration, as the alcohol would be oxidized by the nitric acid. It may, however, be made from nitrotoluene:



*m*-Nitrobenzyl alcohol is produced when concentrated sodium hydroxide solution acts upon *m*-nitrobenzaldehyde; this is another example of the Cannizzaro reaction.



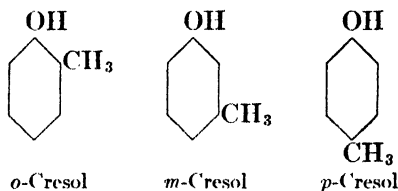
$\beta$ -Phenylethyl alcohol,  $C_6H_5CH_2CH_2OH$ , which occurs in attar of roses, is used in perfumery; for synthesis see pages 572, 580. It has value as

a local anesthetic. Cinnamyl alcohol,  $C_6H_5C(H)=C(H)CH_2OH$ , an example of an unsaturated aromatic alcohol, has a hyacinth odor. It is employed in making perfumes.

## PHENOLS

✓ When a nuclear hydrogen atom of benzene is substituted by the OH group the resulting compound is called a phenol. One or more hydrogens

may be substituted in this way in benzene, naphthalene, etc., giving respectively monohydric, dihydric, and polyhydric phenols, naphthols, etc. The name phenol belongs to the class and also to its simplest member,  $C_6H_5OH$ , formed from benzene. The homologs of phenol exist in three or more modifications. Formulas of the cresols, compounds which stand next to phenol in the homologous series, are as follows:



These compounds are isomeric with benzyl alcohol,  $C_6H_5CH_2OH$ .

We have seen that the aromatic alcohols, in which OH is located on a side-chain, behave like aliphatic alcohols. When the OH group is directly attached to the benzene ring, there are still some points of resemblance to be noted. It will be seen that phenol forms salts, esters, and ethers, in much the same way as an aliphatic or aromatic alcohol. However, the near presence of the benzene ring causes certain marked differences between the two classes of alcohols, both in methods of preparation, and in reactions. These will be pointed out in the progress of the chapter.

#### PHYSICAL AND PHYSIOLOGICAL PROPERTIES OF PHENOLS

Phenol, or carbolic acid, is a colorless solid with a peculiar characteristic odor. Sparingly soluble in water, it dissolves well in the customary organic solvents. It is a violent poison, and has a strongly caustic action, causing the formation of blisters.

It is easily absorbed through the skin or mucous membranes. The toxicity of phenol solutions is probably connected with the precipitation of proteins. Exposed to light and air, phenol is soon colored red. Other monophenols are liquids or colorless solids. Those of higher molecular weight are nearly insoluble in water. They distil without decomposition and are volatile in steam. The majority of these compounds have a pronounced and characteristic odor. The solubility of phenols in water increases with the number of hydroxyl groups, while their volatility in steam becomes correspondingly less. All types, with but few exceptions, are soluble in potassium or sodium hydroxide solution. Most of the phenols have antiseptic action.

Phenol has fair antiseptic value, but the homologs are more powerful antiseptics while less toxic to man. The *phenol coefficient* of a disinfectant is a number representing the concentration of phenol required to destroy an organism in a given time, divided by the concentration of the competing compound needed to destroy the organism in the same time under identical

conditions. This coefficient is useful only when applied to compounds related to phenol.

### MONOHYDRIC PHENOLS

#### *Methods of Preparation*

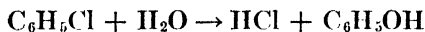
The synthetic methods used to produce the phenols are in marked contrast to those shown for the preparation of alcohols. For the monophenols we have the following methods:

(1) The fusion of a sodium sulfonate with a strong base. Sodium benzenesulfonate by this reaction yields phenol (equation on page 440). This method is used for the commercial preparation of phenol.

(2) The heating of a water solution of a diazonium salt (equation, page 479). This reaction, as is easily seen, offers a means for the transformation of any nitro compound or primary amine to its corresponding hydroxy compound, or through nitration, reduction, and diazotization, any aromatic hydrocarbon may be converted to a hydroxy compound.

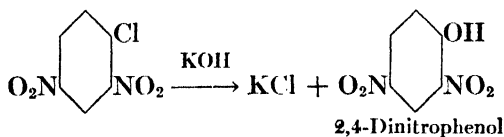
(3a) Within recent years the hydrolysis of benzene halogen compounds has been intensively studied, and this reaction has now been adapted to the commercial production of phenol from chlorobenzene. Chlorobenzene is heated to 320°, pressure of 3000 pounds, with diphenyl ether, sodium carbonate solution, and copper catalyst.

(b) In the Raschig process chlorobenzene is heated to 400–450° with water vapor and a catalyst.



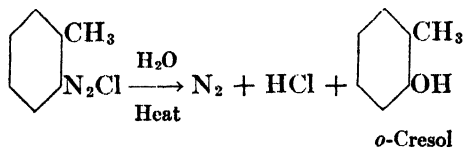
The hydrogen chloride is put into reaction with benzene and air to make additional chlorobenzene (page 430).

When nitro or sulfo group is placed *para* and *ortho* to halogen in the ring, the attachment of the halogen atom is less secure, and hydrolysis occurs readily:

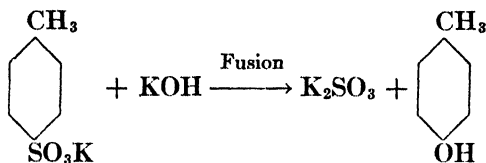


The cresols (*o*, *m*, *p*) are prepared by methods analogous to those just presented.

Examples: Preparation of *o*-cresol from diazotized *o*-toluidine hydrochloride:



Preparation of *p*-cresol from *p*-toluenesulfonic acid salt:

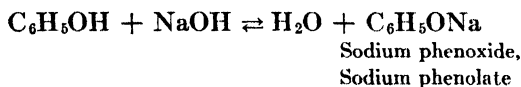


Phenol and the cresols also occur in coal tar, from which they are prepared on the large scale. Cresols are found in beechwood tar.

### REACTIONS OF MONOPHENOLS

The more general reactions of monophenols are as follows:

(1) *Formation of salts (Phenoxides, Phenolates, or Phenates).* Phenol, treated with an equimolecular amount of sodium hydroxide solution, yields sodium phenoxide upon evaporation of the water:

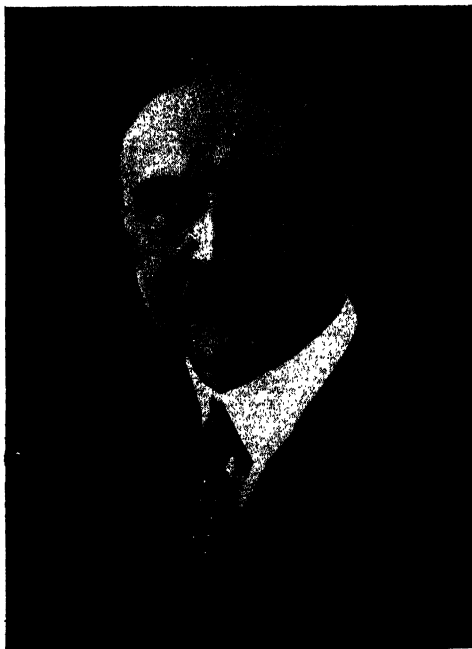


Salts of phenols so prepared are similar in structure to aliphatic alkoxides, but they are stable in water solution, in contradistinction to salts of aliphatic alcohols. Evaporation of their water solutions to obtain the phenoxides is a practical measure, while the evaporation of a solution of an alkoxide might cause distillation of the alcohol to take place.

Aromatic phenols differ from aliphatic alcohols in their possession of marked acid properties. Thus to form the sodium salt we note it is not necessary to use metallic sodium. A solution of phenol will affect litmus paper, but is a weaker acid than carbonic acid, and therefore will not displace it from its salts. Stated another way, phenol is insoluble in a solution of sodium carbonate. This allows us to separate phenols from the carboxylic and sulfonic acids, which are of course soluble in sodium carbonate solution. The acidic nature of phenol is enhanced by the introduction of nitro groups, especially when they are *para* and *ortho* to OH. Picric acid (page 509) is considerably stronger as an acid than is carbonic acid. The following representative ionization constants bear this out.

	Ionization Constants
Water.....	1 $\times 10^{-14}$
Ethanol.....	7.3 $\times 10^{-20}$
Phenol.....	1.3 $\times 10^{-10}$
<i>p</i> -Nitrophenol.....	6.9 $\times 10^{-8}$
Carbonic acid (first hydrogen).....	3.0 $\times 10^{-7}$
Acetic acid.....	1.75 $\times 10^{-5}$
2,4-Dinitrophenol.....	9.6 $\times 10^{-5}$
Picric acid.....	1.6 $\times 10^{-1}$

EDWARD C. FRANKLIN. (1862-1937, American.) An outstanding teacher and research worker. Author of the recent monograph on the nitrogen system of compounds. He was professor of chemistry at the University of Kansas and later at Stanford University. See *Ind. Eng. Chem.*, **19**, 1297 (1927); *J. Chem. Soc.*, (London), **1938**, 583.

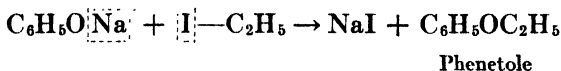


L. H. BAEKELAND. (American, 1863-1944.) Baekeland had his early schooling in Belgium and came to America in 1889. His work has consisted in taking "unworkable" laboratory syntheses in hand, ironing out the difficulties and turning them into large-scale successes. The best known examples are Velox and synthetic resins (Bakelite). See *Ind. Eng. Chem.*, **20**, 1274 (1928); (News Edition), **20**, 1681 (1942).



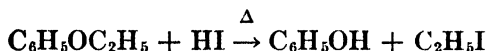
The acid-forming ability of the negative phenyl and nitro groups is well illustrated here.

(2) *Formation of ethers; mixed and simple.* The reaction of a salt of phenol with an alkyl halide gives a mixed ether:

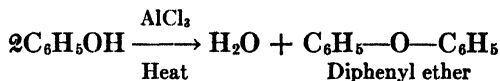


This is an extension of the Williamson reaction (page 123). Anisole,  $\text{C}_6\text{H}_5\text{OCH}_3$ , is formed by a similar reaction with methyl iodide, or with methyl sulfate. If anisole is made from phenyl bromide and sodium methoxide, it is necessary to apply a temperature of over  $200^\circ$  for a long time, heating the materials in a sealed tube under pressure. This is another illustration of the lack of reactivity of aryl halides as compared with alkyl halides.

Ethers like phenetole and anisole hydrolyze with difficulty when heated. With hydriodic acid they yield *alkyl halide* and phenol:

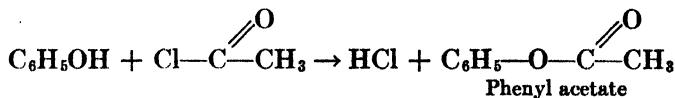


Simple aromatic ethers may be formed by heating phenols with aluminum chloride or zinc chloride:



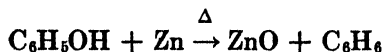
This type of ether resists hydrolysis to a marked degree and is unacted upon by hydrogen iodide even at elevated temperatures. It may, however, be split by treatment with sodium in liquid ammonia; this also applies to its substitution products. Diphenyl ether is used as a boiler fluid (Dow-therm) because of its stability at high temperatures. Anisole, phenetole, and diphenyl ether have fragrant pleasant odors, and are used in synthetic perfumes. Derivatives of the first two will receive consideration in a later paragraph.

(3) *Formation of esters.* Phenols do not form esters directly with organic acids as do alcohols. One uses instead the acid anhydrides or acyl chlorides.

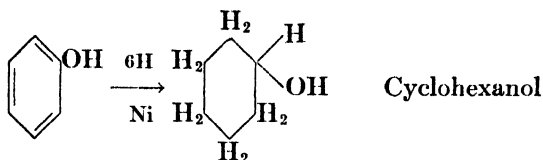


Such esters are very easily hydrolyzed to their constituents.

(4) *Reduction.* Phenol, distilled with zinc dust, is reduced to benzene:



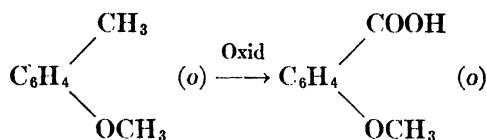
Cresols are similarly converted to toluene. Catalytic reduction of phenol, using hydrogen and a nickel catalyst at  $160^\circ$  gives cyclohexanol.



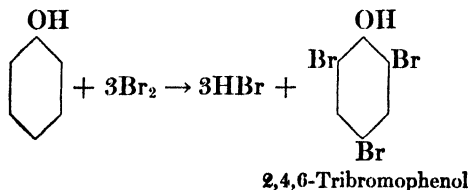
This is used in the commercial production of adipic acid (page 252).

(5) *Oxidation.* Like the aliphatic tertiary alcohols, the phenols have the grouping  $\equiv\text{C}-\text{OH}$ . A certain likeness is observed when these compounds are oxidized; neither aldehyde, ketone, nor acid is produced. Severe oxidation ruptures the benzene ring, yielding acids with lesser carbon content than phenol; this behavior is characteristic of tertiary alcohols.

The oxidation of cresols by chromic acid is facilitated by the protection of the OH group by alkyl or acyl substitution. Oxidation then converts the  $\text{CH}_3$  group to carboxyl. In the absence of such protection oxidation is difficult. *o*-Cresol when methylated is oxidized to the corresponding ether-acid:



(6) *Action of halogens upon phenol.* Substitution by halogen takes place more easily with a phenol than with a hydrocarbon:

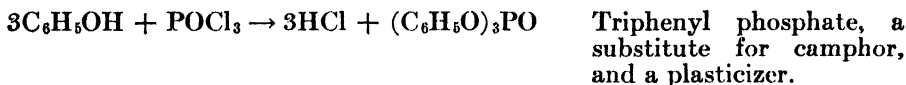


In fact tribromophenol forms at once when bromine-water acts upon phenol. (Note similarity to the reaction of aniline and bromine, page 471.) Its formation may be used as a test for phenol, as tribromoaniline is used for aniline, both derivatives being crystalline solids of definite melting point. The coloration produced by ferric chloride solution may be used as an indication of the presence of a phenol. With this reagent phenol itself gives a violet solution, while the cresols give a blue color. Since ferric chloride yields colored solutions with other compounds than phenols, the test is not specific, but it is often helpful in analytical work (see page 775).

(7) *Reaction with phosphorus pentachloride.* This reagent produces chlorobenzene from phenol. The reaction is not practical for the yield is very low. Nitrophenols give better results.

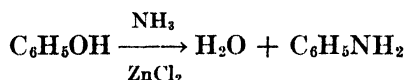


In addition to this reaction, which is typical of aliphatic alcohols, the following side-reaction occurs. Although this is also true for aliphatic alcohols, the side-reaction in that case is not so important as with phenols:



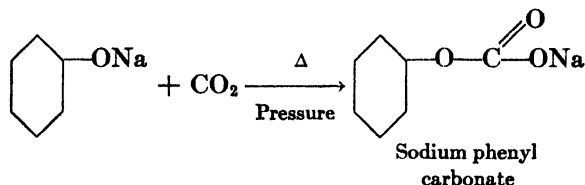
Phenol, in reaction with phosphorus trichloride, similarly yields  $(\text{C}_6\text{H}_5\text{O})_3\text{P}$ , together with  $(\text{C}_6\text{H}_5\text{O})_2\text{PCl}$  and  $(\text{C}_6\text{H}_5\text{O})\text{PCl}_2$ .

(8) *Production of an amine from a phenol.* Phenol heated in the presence of ammonia and zinc chloride exchanges OH group for  $\text{NH}_2$ :

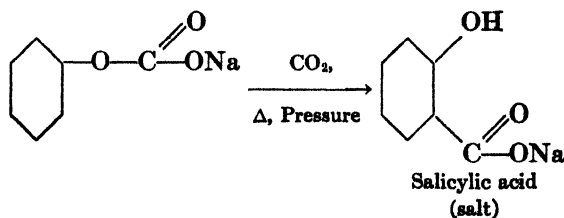


The polyphenols and the naphthols undergo this reaction more readily than do phenols.

(9) *The Kolbe and Schmitt reaction.* When sodium phenoxide is treated with carbon dioxide under pressure, at a temperature of  $130^\circ$ , absorption of carbon dioxide takes place:



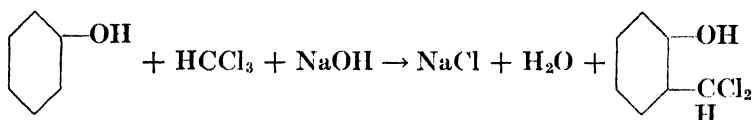
Sodium phenyl carbonate, the product of this reaction, undergoes rearrangement when in the presence of carbon dioxide under pressure. The final product of the rearrangement is the sodium salt of *o*-carboxyphenol (salicylic acid), from which free salicylic acid is obtained by treatment with a mineral acid:



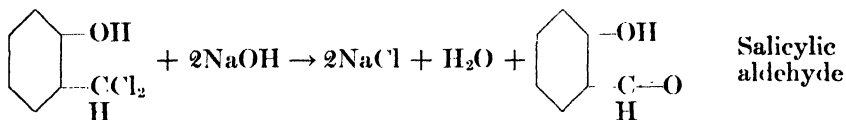
This reaction, on the surface at least, resembles the rearrangements of substituted anilines previously discussed (page 473). In the Kolbe-Schmitt synthesis the shift is generally to the *ortho* position. However we note that heating of potassium phenyl carbonate to  $150^\circ$  gives salicylic acid, but this tends to shift to the *para* acid. At a temperature of  $220^\circ$  only the *para* acid is obtained (page 529). The Kolbe reaction has wide application. Polyhydroxy compounds react readily, also ethers of phenols, also naphthols.

Salicylic acid and its derivatives are taken up in the chapter on acids (page 529). They are compounds of great usefulness.

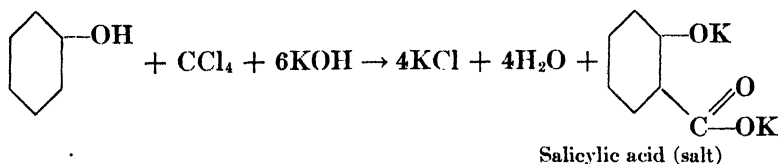
(10) *Reimer and Tiemann reaction. Formation of a phenol aldehyde.* The presence of concentrated sodium hydroxide solution induces a reaction between phenol and chloroform, by means of which the chloroform residue attaches to the benzene ring, mainly *ortho* to the hydroxyl group:



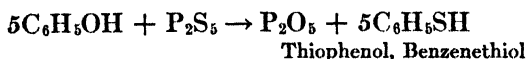
The intermediate compound is hydrolyzed by the excess sodium hydroxide, producing, finally, salicylic aldehyde:



This synthesis, like that of Kolbe, may be applied not only to monophenols but to polyphenols as well, giving rise to numbers of useful derivatives. By a slight modification, using carbon tetrachloride for chloroform, phenol may be converted to salicylic acid:

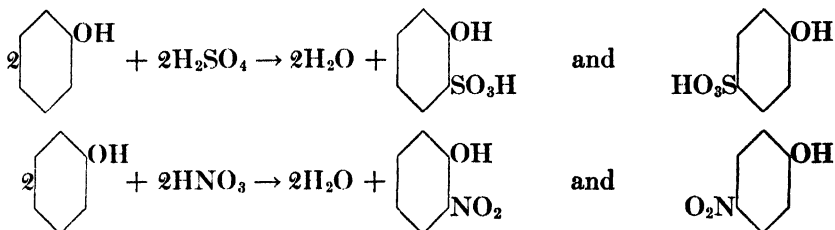


(11) *Formation of thiophenol.* Phosphorus pentasulfide reacts upon phenol, causing exchange of SH for OH group:



Thiophenol is an ill smelling liquid. Like phenol it has caustic action upon the skin. Its oxidation yields benzenesulfonic acid (page 438).

(12) *Action of nitric and sulfuric acids.* Sulfuric and nitric acids do not form esters with phenol, as might be expected by analogy with the aliphatic alcohols. Instead, hydrogen of the benzene ring is substituted by sulfo or nitro groups, the presence of OH making such substitution much easier than with benzene. We have noted in aniline and toluene that the  $\text{NH}_2$  and  $\text{CH}_3$  groups work to aid substitution.

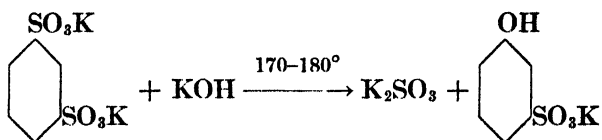


The *p*- and *o*-nitrophenols are formed when phenol is treated with cold dilute nitric acid, or from the *p*- and *o*-nitrochlorobenzenes by hydrolysis.

Distillation with steam removes the *ortho* compound from the *para* which is nonvolatile in steam. *o*-Nitrophenol is a yellow solid, whose odor is reminiscent of phenol and nitrobenzene. It dissolves in alkali to give a red solution. *p*-Nitrophenol is colorless or very light yellow, giving dark orange solutions in alkali. Both nitrophenols are stronger acids than phenol. *m*-Nitrophenol is not formed by direct nitration, but from *m*-nitroaniline through the diazo reaction.

2,4-Dinitrophenol has been found to greatly increase the rate of metabolism when ingested, and was for some time used in the treatment of obesity. The compound has harmful side-effects, however, and its use has been abandoned. 1-Methyl-2-hydroxy-3,5-dinitrobenzene has an even greater effect on the metabolic rate.

The phenol sulfonic acids, *para* and *ortho*, are formed through the direct sulfonation of phenol, the *meta* acid by careful treatment of *m*-benzene-disulfonic acid with potassium hydroxide:

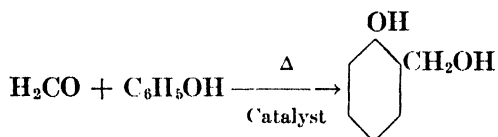


The *p*-phenolsulfonic acid is more stable than the *ortho* compound and is formed from the latter by treatment with hot dilute sulfuric acid. *o*-Phenolsulfonic acid (Aseptol) is an antiseptic.

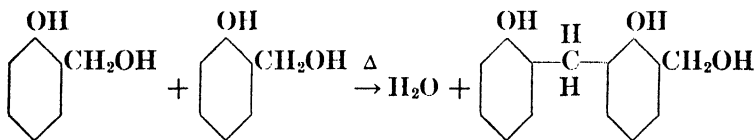
(13) *Reaction with formaldehyde.* Phenol condenses with formaldehyde, or with hexamethylenetetramine, to form products whose chemical make-up is not yet perfectly clear, but which are extremely valuable in many widely varied fields.

If the condensation has not progressed very far, the product is soluble in organic solvents to form a varnish or lacquer. The product of more complete condensation is hard and firm. It is capable of being molded to various shapes; moreover it is resistant to heat, water, and acids, and a non-conductor of electricity. These condensation products are brought upon the market as Bakelite, Resinox, Durez, etc. Such materials are universally applied in making radio parts, magneto parts, pipe stems, cigarette holders, fan blades, airplane and automobile parts, and many other pieces formerly fabricated of hard rubber, wood, metal, or glass. The principal use of phenol is for the manufacture of these synthetic resins.

The initial reaction in Bakelite formation is between formaldehyde and phenol:

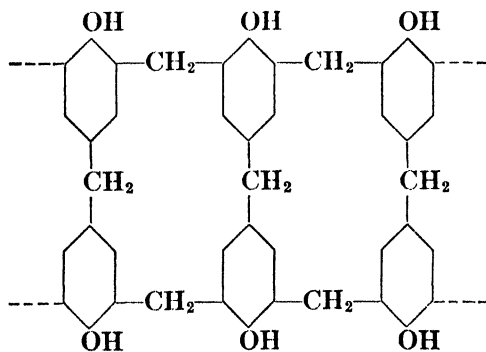


This is followed by reaction between molecules of the newly created intermediate:



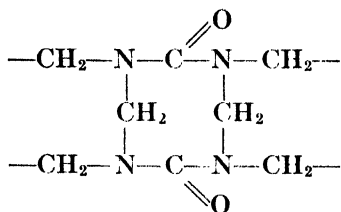
Further reaction of this kind would lead to the production of a linear polymer of the type discussed on pages 150, 255. Such chains exist, but they are *cross-linked* by condensation of formaldehyde between carbon atoms *para* to hydroxyl groups.

Following is a possible formula for a portion of the final complex polymer:



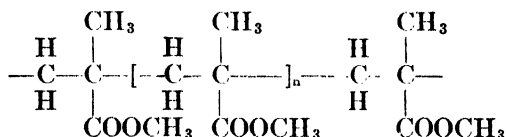
Phenolic resins are also made from phenol, cresol, etc., and furaldehyde, and other aldehydes.



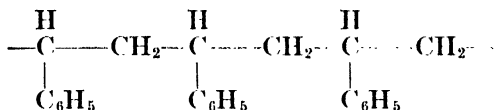


*Phenol-formaldehyde Resins.* See page 502.

*Acrylate Resins.* The polymerization of  $\alpha$ -methylacrylic acid and its methyl ester were mentioned on page 180. Methyl acrylate is also used for resin production. Proposed formula for polymethyl methacrylate is:



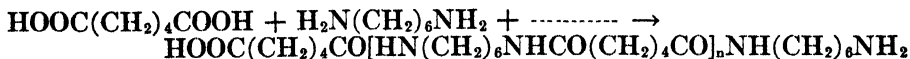
*Polystyrene Resins.* Polystyrene is thermoplastic and has high resistance to acids and alkalis. The linear chain in the polymer is probably:



Hardness of the resins is increased by copolymerization with *p*-divinylbenzene. The effect of the copolymerization probably rests upon reactions which form cross links in the polymer.

*Alkyd Resins.* These are prepared from the interaction of acids and alcohols (in general, polycarboxylic acids and polyhydroxy alcohols). The glyptals, made from phthalic anhydride and glycerol, form an important class (see page 533). Other alkyds are made from sebacic acid, maleic anhydride, succinic acid, with ethylene glycol, diethylene glycol, and other alcohols (see page 255).

*Nylon.* This is a general name used for all fiber-forming materials of polyamide structure. Many different nylons are now available. One of these is a linear polymer formed from adipic acid and hexamethylenediamine. Hexamethylenediamine is made from adipic acid (page 252) by the following steps: (1) transformation to adipamide by treatment with ammonia (heat, pressure); (2) reduction of adipamide by catalytic hydrogenation.

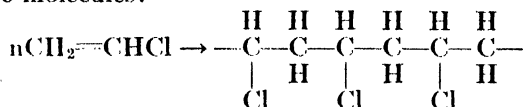


Nylon is thermoplastic. For production of thread the melted material is forced through dies in fine filament form. The filaments are then



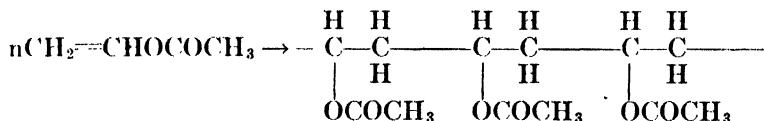
stretched; this has the effect of lining up the long molecules into parallel bundles, thereby increasing the tensile strength and elasticity of the filament.

*Vinyl chloride resins* contain a linear chain complex formed by addition of vinyl chloride molecules:

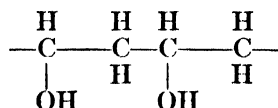


The resins are thermoplastic; they are used for flexible tubing, gaskets, other purposes in which resistance to corrosion is important.

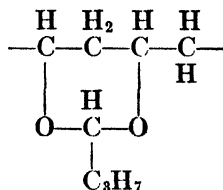
*Vinyl acetate resins* contain the chain:



They are thermoplastic; used largely for adhesive purposes (binder for drinking cups, food cartons); metallic lacquers. *The hydrolysis of polyvinyl acetate* gives polyvinyl alcohol:

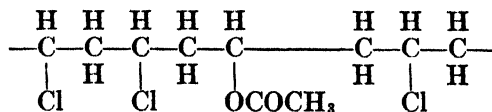


This in reacting with an aldehyde gives a polyacetal. A section of the polyvinyl butyral molecule is:



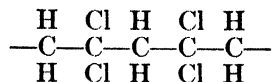
The resin made of polyvinyl butyral was largely used as the interlayer of safety glass. Present uses in World War II include: hospital sheeting, life rafts, surgical plasters, water bags. Formaldehyde and acetaldehyde are condensed with polyvinyl alcohol as shown above to give useful resins.

*Copolymerization of vinyl chloride and vinyl acetate* in various proportions gives a series of plastics. A possible structure for a portion of one of the molecules is:



*Vinyon* (a textile) is of this type; *Koroseal*, widely used in shower curtains, raincoats, etc., is made from vinyl chloride.

*Vinylidene chloride*,  $\text{CH}_2=\text{CCl}_2$ , is polymerized to give a linear molecule, a portion of which may be:



When the molecules are oriented in parallel fashion by suitable treatment the material has great tensile strength. It is made in rods and tubes, etc., used for outdoor furniture, seat covers, flexible piping. Saran is a trade name.

*Copolymerization of vinyl chloride and vinylidene chloride* is also employed for resin manufacture.

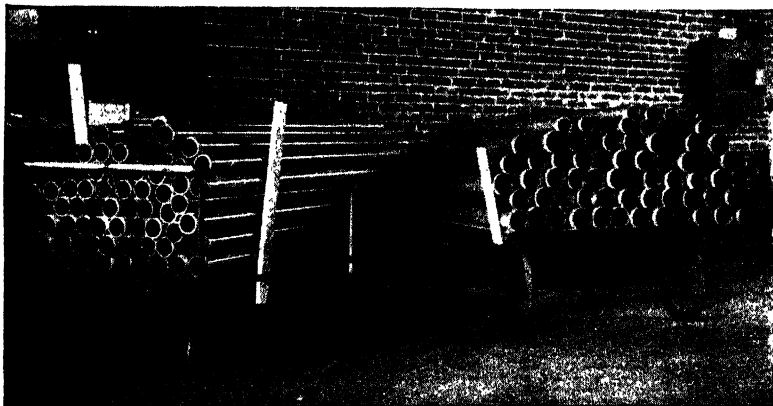


FIG. 83.—Synthetic resin pipe for use in chemical plants. (*Ind. and Eng. Chemistry*.)

*Petroleum resins* are made by treatment with aluminum chloride of mixtures obtained in the cracking of low molecular weight alkanes such as propane or butane. The resins are unsaturated and oxidize readily when dissolved in a solvent and exposed in a thin film; hence they are useful in quick-drying varnishes.

Other materials used in making plastics include cellulose acetate, Galalith (formaldehyde-casein product), ethylene dichloride (Thiokol) (page 625). Ethylene dihalides heated with certain aromatic hydrocarbons of formula  $\text{RC}_6\text{H}_4\text{R}_1$  in the presence of aluminum chloride, give plastics (A-X-F), useful for compounding with rubber or Neoprene. Soybean protein is used with formaldehyde to make a thermoplastic resin; soybean protein may also be used in connection with phenol and formaldehyde.

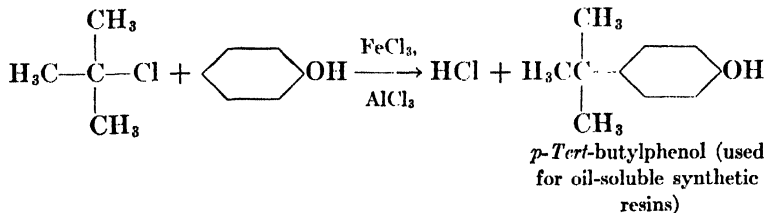
*Ester gum* is used in large amounts to blend with other resins in lacquer formation. It is made by esterifying rosin acids (chiefly abietic acid) with glycerol. Many of the newer plastics are made by the use of rubber as a starting material (Plioform).

In the fabrication of synthetic resins, plasticizers are used to prevent embrittlement, also fillers and coloring materials. A variety of catalysts is

used to aid the polymerization reactions. Not only are the resins used for production of solid objects; many coating compositions are made by dissolving synthetic resins in suitable solvent mixtures.

Space limitations forbid any attempt to discuss the methods\* by which these resins are brought to the market; this material will be found in the references at the end of the chapter.

(14) *Alkylation of phenol*. If phenol is treated with an alkyl halide in presence of ferric chloride or aluminum chloride, alkylation occurs:



*p*-Tert-amylphenol (Pentaphen) is a compound of the type under discussion. It is used to make oil-soluble synthetic resins, as a plasticizer for cellulose nitrate, and as a bactericide.

It has been noted that certain alkyl-phenyl ethers rearrange in presence of aluminum chloride; the OH group is reformed and the alkyl group migrates to the ring. Boron fluoride also promotes this reaction.

For condensation reactions of phenols leading to the production of dyes, see pages 535 and 686.

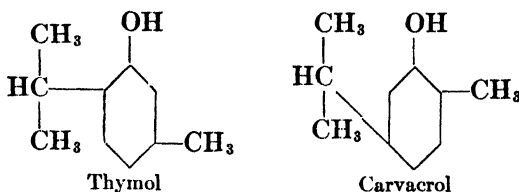
#### EXAMPLES OF MONOHYDRIC PHENOLS

**Phenol** (Carbolic acid) and the cresols have already been considered at some length. Aside from their value for synthetic work, which is considerable, these substances have wide employment as antiseptics and disinfectants. For such purposes the cresols are more effective and at the same time less poisonous than phenol. Lysol is a mixture of cresols in soap solution, used as a disinfectant, especially in hospitals.

**Thymol** is a natural monophenol, found in oil of mint and of thyme. It has a considerable germicidal power, and possesses an agreeable odor. It is used in the treatment of hookworm, also in tooth pastes, mouth washes, etc. It is sometimes used to preserve urine. Diiododithymol (Aristol) is a substitute for iodoform. It is a reddish-brown, tasteless powder (see page 642). *m*-Cresol is produced when thymol is heated with P<sub>2</sub>O<sub>5</sub>.

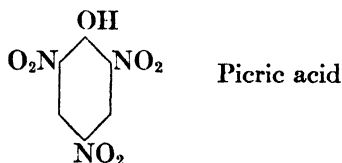
**Carvacrol**, like thymol, is found in essential oils of plants. It is isomeric with thymol, and is a powerful antiseptic. Both of these substances are closely related to the terpenes. Carvacrol heated with P<sub>2</sub>O<sub>5</sub> or AlCl<sub>3</sub> gives *o*-cresol.

\* Some idea of the complexity in the resin field will be gained by reading Reference 19. The plastics industry of the United States manufactured over 500,000,000 lbs. in 1941. For interesting data from experimental work, see Reference number 9, page 518.



## SUBSTITUTED PHENOLS, ETC.

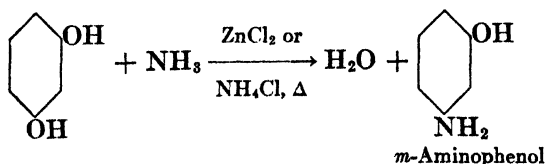
**Nitrophenols.** Several nitrophenols have already been mentioned (mononitrophenols, page 502, dinitrophenol, page 449). Picric acid, 2,4,6-trinitrophenol, is by far the most important of the nitrophenols.\* It may be prepared by nitration of phenol in the presence of sulfuric acid at 100°, by the simultaneous nitration and oxidation of benzene by nitric acid, using mercuric nitrate as a catalyst, or by nitration of 2,4-dinitrophenol (made from chlorobenzene by nitration and hydrolysis).



Due to the presence of the three nitro groups, trinitrophenol shows a distinctly acid character and readily forms salts. Ammonium picrate is used in the manufacture of explosives, however some of the metal salts of picric acid are dangerously explosive. The acid itself is also a powerful explosive. In addition to such use it functions as an antiseptic, and as a dye (yellow) for silk and wool.

Picric acid is used as a reagent in a large number of chemical and biochemical tests. It is used in the treatment of burns, as an antiseptic, and otherwise in medicine. With many aromatic hydrocarbons, amines, and phenols, picric acid forms crystalline molecular compounds, often highly colored. Such compounds may usually be purified by recrystallization, and as they generally have sharp melting points, they are used in identifications. Compounds of this type may be split into their components by the use of ammonia or hot water.

**Aminophenols.** These are formed by the reduction of nitrophenols or by the action of ammonia-zinc chloride or ammonium chloride upon the polyphenols:

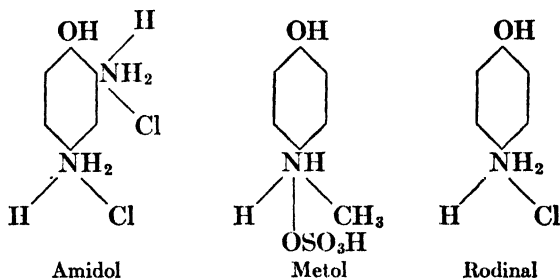


\* The acid has a very bitter taste and is named from the Greek word pikros = bitter.

As we have seen (page 447) *p*-aminophenol is a partial reduction product of nitrobenzene, made by rearrangement of phenylhydroxylamine.

Aminophenols are not soluble in alkali like other phenols, but they form salts with strong acids through action of the amino group, and they may be diazotized. These compounds are colorless solids, which upon exposure to air are soon oxidized to a yellow or brown color. Because of their susceptibility to oxidation, the aminophenols are used as developers in photography. In this role they reduce to metallic silver the silver bromide of the photographic emulsion. Those portions of silver bromide which have been light struck are readily reduced; thus a light and dark image, the "negative," results from the selective action of the developing agent.

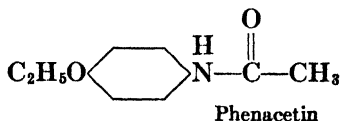
Some aminophenol developers are amidol, metol, and rodinal.



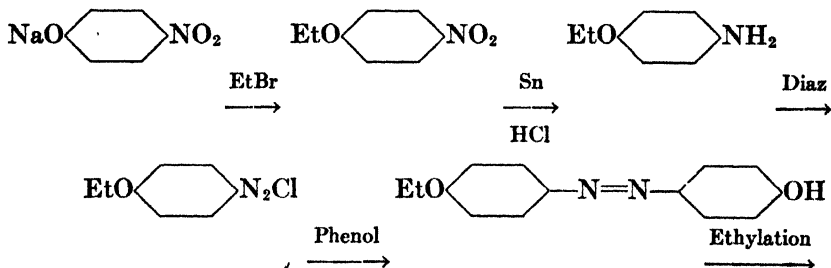
It will be noted that the groups in these compounds are *para* and *ortho* to each other. This again illustrates the point made several times in previous discussion that OH, NH<sub>2</sub>, and CH<sub>3</sub> groups in *para* and *ortho* positions enhance the activity of a compound. *m*-Aminophenol is not easily oxidized.

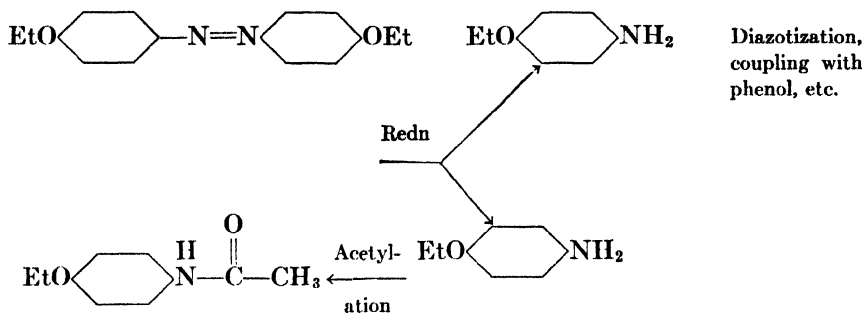
Several of the amino derivatives of phenol ethers have practical importance, e.g.,

**Phenacetin**, acetyl derivative of *p*-aminophenetole (phenetidine). This is a very well known antipyretic compound. It is less toxic than acetanilide.



It is made by an ingenious process shown below in diagrammatic form:



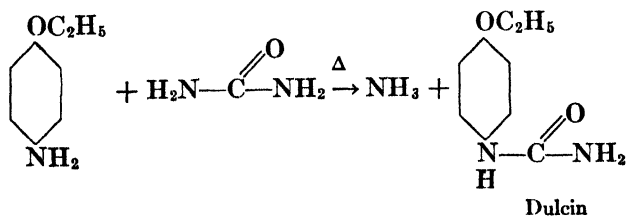


This process enables a molecule of *p*-nitrophenol to do double duty through diazotization and coupling with the cheaper compound phenol.

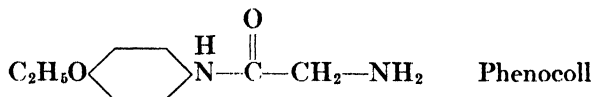
TABLE 37.—PHYSICAL CONSTANTS OF PHENOLIC COMPOUNDS

Name	Formula	M.p., °C.	B.p., °C.	K <sub>A</sub>
Phenol.....	C <sub>6</sub> H <sub>5</sub> OH	42-3	181.4	1.30 × 10 <sup>-10</sup>
Cresol ( <i>o</i> ).....	CH <sub>3</sub> C <sub>6</sub> H <sub>4</sub> OH	30.8	190.8	4.2 × 10 <sup>-8</sup>
Cresol ( <i>m</i> ).....		10.9	202.8	1.7 × 10 <sup>-8</sup>
Cresol ( <i>p</i> ).....		35-6	202	1.1 × 10 <sup>-8</sup>
Chlorophenol ( <i>o</i> ).....	ClC <sub>6</sub> H <sub>4</sub> OH	7	175	3.6 × 10 <sup>-8</sup>
Chlorophenol ( <i>m</i> ).....		28.5	214	
Chlorophenol ( <i>p</i> ).....		41	217	2 × 10 <sup>-8</sup>
Nitrophenol ( <i>o</i> ).....	NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> OH	44-5	214.5	6.5 × 10 <sup>-8</sup>
Nitrophenol ( <i>m</i> ).....		96-7	194 <sup>70</sup>	5.3 × 10 <sup>-8</sup>
Nitrophenol ( <i>p</i> ).....		113-4		6.9 × 10 <sup>-8</sup>
Picric acid.....	(NO <sub>2</sub> ) <sub>3</sub> C <sub>6</sub> H <sub>2</sub> OH	121.8	Exp. > 300	1.6 × 10 <sup>-1</sup>
Pyrocatechol (1,2).....	(OH) <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	104-5	240-5	3.2 × 10 <sup>-10</sup>
Resorcinol (1,3).....		110.7	276.5	6 × 10 <sup>-7</sup>
Hydroquinone (1,4).....		170.3	285 <sup>730</sup>	1.1 × 10 <sup>-10</sup>
Pyrogallol (1,2,3).....	(OH) <sub>3</sub> C <sub>6</sub> H <sub>3</sub>	133-4	309	0.5-2 × 10 <sup>-7</sup>
Hydroxyhydroquinone (1,2,4).....		140.5		
Phloroglucinol (1,3,5).....		209-19	Sub.	0.8-2 × 10 <sup>-7</sup>
α-Naphthol.....	C <sub>10</sub> H <sub>7</sub> OH	96	278-80	1 × 10 <sup>-8</sup>
β-Naphthol.....		122-3	285-6	

**Dulcin** is the carbamyl derivative of phenetidine. It is about two hundred times as sweet as cane sugar, in this way bearing resemblance to saccharin (page 527) and perilla aldoxime (page 763).



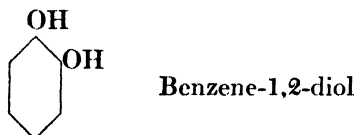
**Phenocoll**, glyceryl derivative of phenetidine, is dispensed in the form of its hydrochloride. It is a remedy for neuralgia, headache, mild fevers.



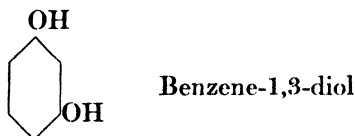
### DIHYDRIC PHENOLS, BENZENEDIOLS

The dihydric phenols (*o*, *m*, *p*) have special names as follows:

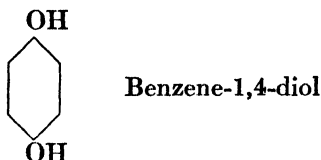
***o*-Dihydroxybenzene**, pyrocatechol, catechol, pyrocatechin. Contained in resins and the sap of various plants; in beechwood tar.



***m*-Dihydroxybenzene**, resorcinol, resorcin. Obtained by heating asafoetida and other resins with potassium hydroxide.

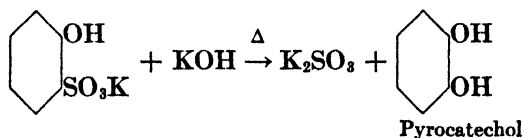


***p*-Dihydroxybenzene**, hydroquinone, quinol. From arbutin, a glucoside (page 736).



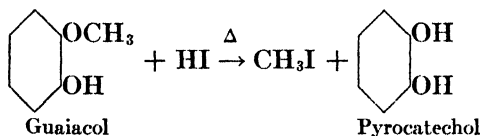
### METHODS OF PREPARATION OF DIHYDRIC PHENOLS

**Pyrocatechol**, *o*-dihydroxybenzene, results from a modification of reaction (1) given for the monophenols (page 495), that is when *o*-phenolsulfonic acid salt is heated with potassium hydroxide:



However, it is usually made from a natural product, guaiacol, found in

beechwood tar. This substance, which is both an ether and a phenol, reverts to catechol when heated with hydriodic acid:



Adrenaline (page 741) is an important derivative of pyrocatechol.

*Resorcinol*, *m*-dihydroxybenzene, is commonly made from *m*-benzene-disulfonic acid salt by fusion with alkali. It is a curious fact that resorcinol also results when *p*-benzenedisulfonic acid is fused with sodium hydroxide. Moreover, certain other *para* and *ortho* derivatives of benzene, when fused with alkali, react to give *m*-dihydroxybenzene. As we have so far tacitly assumed that in all replacement reactions the entering groups take the same positions as those groups being eliminated, it is important that this exception to the general rule should be well noted. Evidently the *m*-dihydroxy compound is more stable than its *para* and *ortho* isomers, and when these compounds are first formed by simple replacement reactions, they undergo a rearrangement to the more stable configuration. (See also *p*-phenol-sulfonic acid, p. 502.)

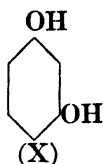
*Hydroquinone* is a reduction product of quinone (page 560) prepared by reducing the latter in water solution with sulfur dioxide.

#### REACTIONS OF DIHYDRIC PHENOLS

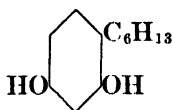
The *para* and *ortho* diphenols are alike in their sensitiveness to oxidation, which makes them effective reducing agents. Pyrocatechol in alkaline solution absorbs atmospheric oxygen. Likewise it readily precipitates metallic silver or platinum from solutions of their salts, hence its use in photography as a developer. Hydroquinone is an even better developer. Hydroquinone belongs to the group of substances known as *antioxidants*. Small amounts of such substances added to reactive compounds delay and prevent auto-oxidation or polymerization reactions.

Resorcinol is not as good a reducing agent as the *para* and *ortho* diphenols. Its chief use is for the production of dyes. The hydrogen marked (X) in the formula, which is *para* to one OH group and *ortho* to the other, is especially active (note activity of *para* hydrogen of dimethylaniline, page 472, and of aniline, page 460). Dyes are readily formed with phthalic anhydride by removal of this hydrogen atom with oxygen of the anhydride (as water). The formula for one of these will be found on page 689. Resorcinol has application in medicine as an antipyretic and antiseptic. Hexylresorcinol ("Caprokol") is used as a urinary antiseptic. It is about 45 times as effective an antiseptic as phenol. This compound is found in the antiseptic marketed as S.T. 37. While not entirely satisfactory as a urinary or local antiseptic, it is used effectively against hookworm.





Resorcinol



Hexylresorcinol

Resorcinol is a valuable reagent in a number of chemical tests. It is sweet.

#### COLOR REACTIONS WITH FERRIC CHLORIDE

Practically all hydroxy compounds react with a solution of ferric chloride to give colored solutions, the colors produced in the case of the phenols being quite intense. The dihydric phenols act as follows:

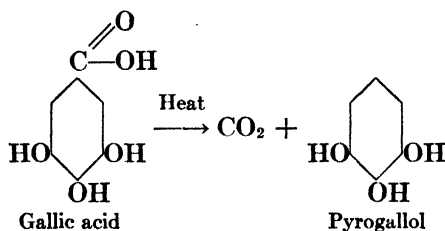
Pyrocatechol with ferric chloride gives a green solution.

Resorcinol gives a violet solution.

Hydroquinone acts as a reducing agent and is partially oxidized to quinone. A green colored addition-product of quinone and hydroquinone, called quinhydrone, is precipitated (page 565).

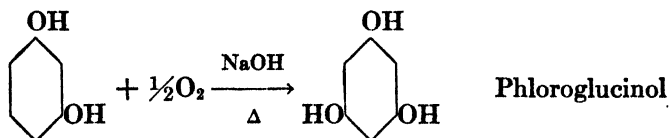
#### TRIHYDRIC PHENOLS, BENZENETHIOLS

Within this series of isomers the most important compound is pyrogallol or pyrogallic acid, 1,2,3-trihydroxybenzene. This may be had from gallic acid, a constituent of gall-nuts, acorns, etc., by the application of heat:



Pyrogallol is oxidized with extreme ease; it is a photographic developer. An alkaline solution quickly absorbs oxygen from a mixture of gases; this property is utilized in gas analysis to determine the oxygen content of a mixture. Ferric chloride gives a red color with a solution of pyrogallol.

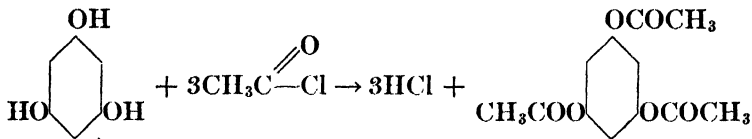
Phloroglucinol, 1,3,5-trihydroxybenzene is a constituent of various glucosides, notably phloridzin. Resorcinol when fused with sodium hydroxide in the presence of oxygen (air) yields phloroglucinol:



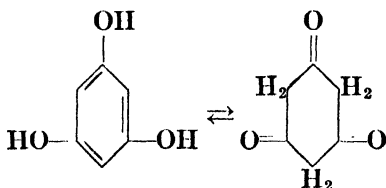
Like pyrogallol this compound is easily oxidized, and its alkaline solutions absorb oxygen. Ferric chloride gives a dark violet solution with phloro-

glucinol. The compound has a sweetish taste (Greek word for sweet = glykos).

When it is treated with an acid halide (anhydride) phloroglucinol forms a triacyl derivative as would be expected:



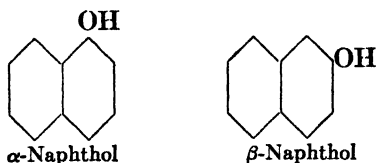
However, we find that hydroxylamine will also react with phloroglucinol to yield a trioxime. This clearly indicates the presence of three keto groups in the molecule. We are thus led to the conclusion that phloroglucinol possesses both a ketone and an alcohol (phenol) structure.



This is another example of tautomerism of the keto-enol type, already discussed with certain aliphatic compounds (page 453). Resorcinol has been shown to act in a similar way.

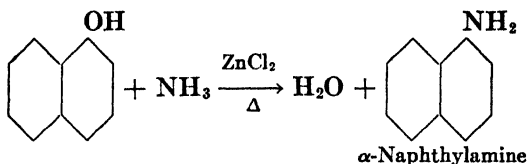
#### NAPHTHOLS

The monohydric compounds derived from naphthalene, called naphthols, have considerable importance due to their use in dye manufacture. Two mononaphthols are possible, i.e.,



They are prepared by methods (1) and (2) applied in the benzene series (page 495).  $\alpha$ -Naphthol is practically insoluble in water, soluble in alcohol and ether. Its odor is like that of phenol. Ferric chloride yields a white precipitate with  $\alpha$ -naphthol.  $\beta$ -Naphthol is soluble in hot water. With ferric chloride a white opalescence is obtained.

The naphthols behave like the polyphenols when treated with ammonia and zinc chloride;  $\text{NH}_2$  is exchanged for  $\text{OH}$ :



A more important method is that of Bucherer. Here the naphthol is treated with ammonium sulfite and ammonia at 150–180° under pressure. The yield is excellent. The reverse substitution of OH for NH<sub>2</sub> can be carried out by treatment of the naphthylamine with a water solution of sodium bisulfite.

The reactions of naphthols with ammonia, with hydrogen chloride, or phosphorus pentachloride proceed more readily than the corresponding reactions with phenols.

The amino and sulfonic derivatives of the naphthols used in dye making are illustrated by several examples on pages 675, 676.

#### REVIEW QUESTIONS

- Write graphic formulas for the following compounds. (a) Di-*o*-tolyl ether; (b) Methyl-*p*-tolylcarbinol; (c) *m*-Nitrobenzyl alcohol; (d) 2,5-Dichlorophenol; (e) Carvacrol.
- Outline and contrast the methods of preparation of benzyl alcohol and of phenol.
- Cite three reactions for benzyl alcohol and three for phenol, which are similar in type.
- Write equation for the preparation of potassium phenoxide and show one of its uses by means of another equation.
- Write equations for the production of the following from phenol: (a) Phenyl propyl ether; (b) Diphenyl ether; (c) Phenyl propionate; (d) Benzene; (e) Chlorobenzene; (f) Aniline.
- Outline by the use of equations the methods of preparing salicylic acid from phenol.
- How may benzenesulfonic acid be synthesized from phenol?
- Show methods of preparation of *o*-, *m*-, and *p*-dihydroxy benzenes.
- Give the practical uses of five phenol derivatives, with equations for the synthesis of each compound.
- How could the following compounds be distinguished from each other: (a) C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>OH and C<sub>6</sub>H<sub>4</sub>CH<sub>3</sub>(OH)? (b) Aniline and phenol?
- How could one separate a mixture of phenol, aniline, nitrobenzene, and benzene, securing each of these in pure condition?
- How may an organic acid be separated from phenol?
- Show how phenol may be made from: (a) Benzene; (b) Benzenesulfonic acid; (c) Aniline.
- Which is more acidic, *o*-cresol or benzyl alcohol, its isomer? How would you prove the point?
- Explain the fact that phloroglucinol possesses reactions of both ketone and alcohol character.
- Give two syntheses for anisole, beginning with nitrobenzene, and with salicylic acid.
- Discuss and show by equations the "multiplication" of *p*-nitrophenol in the making of phenacetin.
- Show a method not given in this chapter for making dulcin from phenetidine.
- In a laboratory synthesis of phenol the product was obtained in the final step in an alkaline solution which was extracted with ether. The yield was very low. Was anything overlooked?
- Make a list of the rearrangements which have been presented in this chapter.
- Explain the importance of the Bucherer reaction in the preparation of *beta*-naphthylamine.

22. A teacher of organic chemistry has on hand ample supplies of the following materials: water, alcohol, ether, benzene, hydrochloric acid, nitric acid, sulfuric acid, acetic acid, sodium hydroxide, sodium nitrite, tin, phosphorus pentachloride, aluminum chloride. What aromatic preparations can he assign for the laboratory? (Confine your list to preparations mentioned in this and preceding chapters.)
23. What compound would, after short treatment with hot NaOH solution, yield *p*-chlorobenzyl alcohol?
24. Cite facts which show that reactions which involve high temperature treatment with alkali should not be used to determine the position of substituting groups on a benzene ring.
25. Show by equations the behavior of the following reagents with phenol: (a) NaOH solution; (b) Sulfuric acid; (c) Bromine; (d)  $\text{PCl}_3$ .
26. Tell how to separate: phenol from nitrobenzene; phenol from aniline; phenol from benzoic acid; water from phenol.
27. List medical uses of all suitable compounds mentioned in this chapter.
28. Illustrate by means of equations the following reactions of cinnamyl alcohol. (a) Esterification; (b) Formation of a saturated alcohol; (c) Oxidation (show two types); (d) Addition; (e) Salt formation.
29. Outline the necessary conditions and chemicals for the following conversions. (a) Benzene to triphenylcarbinol; (b) Toluene to *p*-cresol; (c) Benzene to phloroglucinol; (d) Benzene to *p*-nitrobenzaldehyde; (e) Naphthalene to  $\alpha$ -naphthylamine.
30. Write graphic formulas for the compounds which would be formed in the treatment of: (a) Sodium *m*-toluenesulfonate with solid NaOH (fusion); (b) Thymol with  $\text{P}_2\text{O}_5$ ; (c) The product of (b) with a strong oxidizing agent; (d) Sodium benzenesulfonate with KCN (fusion); (e) The product of (d) with a hot solution of NaOH; (f) The product of (e) with  $\text{CH}_3\text{I}$ .
31. Complete the following equations.
- (a) *p*-Cresol + Na  $\rightarrow$
- NaOH
- (b)  $\text{C}_6\text{H}_5\text{OH} + \text{CH}_3\text{I} \longrightarrow$
- (c) *m*-Cresol + acetic anhydride  $\rightarrow$
- (d)  $\text{C}_6\text{H}_5\text{OH} + \text{C}_6\text{H}_5\text{NCO} \rightarrow$
- $\Delta$
- (e)  $\text{C}_6\text{H}_5\text{OCH}_3 + \text{HI} \rightarrow$
- $220^\circ$     HCl
- (f)  $\text{C}_6\text{H}_5\text{OK} + \text{CO}_2 \longrightarrow \text{X} \longrightarrow$
- (g)  $\text{C}_6\text{H}_5\text{OH} + \text{CCl}_4 + \text{KOH} \rightarrow$
32. What tests would enable one to distinguish the following compounds from each other?
- (a) *o*-Cresol, benzoic acid, *n*-octyl alcohol;
- (b) Resorcinol, naphthalene, diphenylamine;
- (c) Benzyl alcohol, *o*-toluidine, anisole.
33. A certain natural organic compound contains 75% C, 6.82% H, and 18.18% O. If it is heated with dilute alkali for a time, reaction takes place. Acidification of the mixture allows the isolation of two compounds, (A) and (B). (A) is acidic. It contains 40.0% C, 6.67% H, and 53.32% O. A 0.20 g. sample requires 37.03 cc. of 0.09 N NaOH solution for its neutralization. Compound (B) contains 80.6% C, 7.46% H, and 11.94% O. Mild oxidation yields the compound (C) which forms a bisulfite compound and which may be reduced to a compound (D) containing 79.41% C. Vigorous oxidation of (B) yields the acid (E), m.p.,  $121 + ^\circ\text{C}$ . This contains 68.84% C, 4.92% H, and 26.22% O. Its sodium salt contains 15.97% Na. Explain the chemistry discussed here and give the structure of the original compound.

34. An organic compound (A) of empirical formula  $C_7H_7O$  has the following properties: it reacts with hydroxylamine to form an oxime (m.p.,  $155^\circ$ ; exp.); with ferric chloride solution it gives a violet color; one mole of (A) reacts with three moles of acetic anhydride to give a new compound and three moles of acetic acid. Attempt to prove the structure of (A). Is any further information needed? If so, outline definitely any necessary additional facts.

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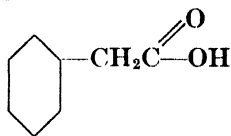
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## CHAPTER XXVII

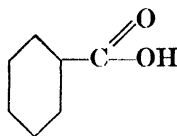
### AROMATIC ACIDS

In the aromatic acids we find one or more of the carboxyl groups characteristic of organic acids in general, either as part of a side-chain, or directly attached to an aromatic nucleus, such as benzene, naphthalene, etc.

Examples:



Phenylacetic acid,  
Phenylethanoic acid



Benzoic acid,  
Benzenecarboxylic acid,  
Phenylformic acid

A compound like phenylacetic acid is essentially aliphatic in nature, but because one of its alkyl hydrogens has been substituted by a benzene ring, we think of it as an aromatic compound. This is natural, since the substituted benzene ring has a molecular weight greater than that of the acetic acid itself, and because nuclear derivatives may readily be formed from such a compound. Mono- and dicarboxylic acids of the type of benzoic acid are the most important of the series of aromatic acids.

#### MONOCARBOXYLIC ACIDS

**Physical Properties.** Benzoic acid is a colorless solid, sparingly soluble in cold water, but sufficiently soluble in hot water to allow its crystallization from a water solution. It is freely soluble in alcohol and ether. Benzoic acid is volatile in steam, also it sublimes at  $100^{\circ}$ , a temperature some  $20^{\circ}$  below its melting point. The vapor is irritating, and causes coughing and sneezing. Many of the salts of benzoic acid are quite soluble in water. The sodium salt has an antiseptic action and in the past has been much used in preserving foods. It is used in the treatment of gout, rheumatism, influenza. Other aromatic monocarboxylic acids are crystalline solids, with properties much like those of benzoic acid.

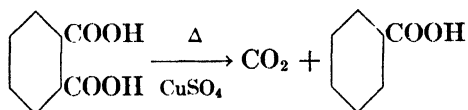
**Preparation.** Benzoic acid occurs in the free state in several resins, notably gum benzoin, and may be separated from the other material by sublimation. Derivatives of this acid are found in Tolu and Peru balsams. Other acids of this series also have natural sources. A large number of methods are known by which these acids may be synthesized. Several of the methods are new, while the majority have already been presented in other

chapters. These latter are again listed for the benefit of reviewing the basic chemistry they represent.

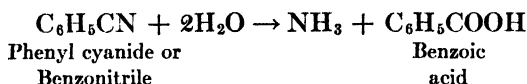
(1) **Acids from the oxidation of hydrocarbons.** While we do not find it practical to prepare acetic acid by oxidizing ethane, a somewhat analogous reaction is quite feasible in the aromatic series. Thus, the oxidation of toluene yields benzoic acid (for equation, see page 413). The oxidation proceeds more readily when the side-chain has been substituted. Benzyl chloride,  $\text{C}_6\text{H}_5\text{CH}_2\text{Cl}$ , benzyl alcohol,  $\text{C}_6\text{H}_5\text{CH}_2\text{OH}$ , or benzaldehyde,  $\text{C}_6\text{H}_5\text{CHO}$ , may thus be used instead of toluene. The oxidation of the two latter substances to benzoic acid is seen to tally the oxidation of ethyl alcohol or acetaldehyde to acetic acid.

It is important to remember that any alkyl side-chain upon oxidation yields the carboxyl group. This applies to both saturated and unsaturated chains. Benzoic acid would then be formed from the oxidation of any suitable alcohol, aldehyde, ketone, or phenyl fatty acid.\* When two or more side-chains are present, one alone may be oxidized to give an alkyl-substituted acid, as shown below.

(2) **An important commercial method for preparation of benzoic acid** involves the decarboxylation of phthalic acid. This is accomplished by passing steam and phthalic anhydride (page 534) heated to  $275\text{--}300^\circ$  over a copper catalyst. Some of the resulting phthalic acid decomposes to lose carbon dioxide.

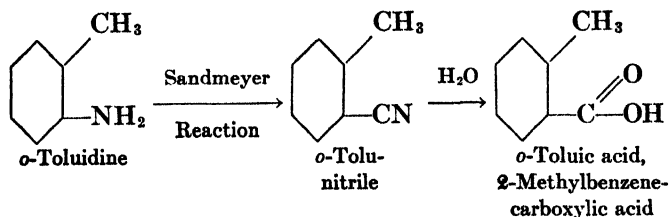


(3) **Preparation through hydrolysis of benzene derivatives.** Benzoic acid and other aromatic acids result from the hydrolysis of their nitriles:



The nitrile may be made by the Sandmeyer reaction (page 483) or from the corresponding sulfonic acid (page 440); thus, through the above reaction, we are enabled to prepare a carboxylic acid from any aromatic hydrocarbon, sulfonic acid, nitro compound, or primary amine.

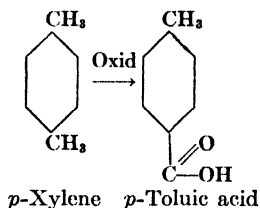
Example: Toluic acid from *o*-Toluidine:



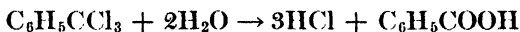
\* A very few exceptions to this general statement have been found.



Toluic acids may also be made by the partial oxidation of the corresponding xylenes. Thus, *p*-xylene oxidized with dilute nitric acid yields *p*-toluic acid:



Benzoic acid may be made on the large scale by the hydrolysis of benzylidene chloride:

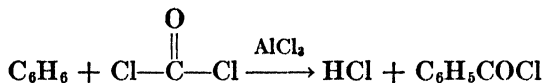


This hydrolysis is accomplished by the use of calcium hydroxide, which produces the calcium salt of benzoic acid. Upon addition of a mineral acid, benzoic acid is precipitated from the solution.

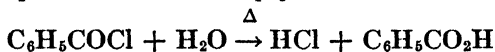
Esters, amides, and acid halides of aromatic acids liberate the free acid when they are subjected to hydrolysis. In this respect, they react precisely like aliphatic esters and amides, etc.

(4) We have seen that a sulfonic acid may be transformed to a carboxylic acid by first making the nitrile from it. The direct change from  $\text{SO}_3\text{H}$  to  $\text{CO}_2\text{H}$  is brought about by the use of sodium formate (Victor Meyer method, page 440).

(5) The Friedel and Crafts reaction allows the formation of a carboxylic acid from a hydrocarbon and phosgene, using aluminum chloride as a catalyst:

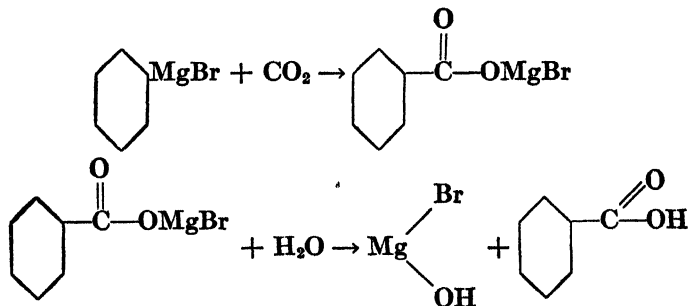


The acid chloride produced in this step yields its acid when hydrolyzed:



As shown on page 578, this reaction may also produce diphenyl ketone.

(6) An aromatic Grignard reagent forms a carboxylic acid when acted upon by carbon dioxide:



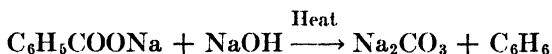
The Grignard reaction is taken up in detail on page 569, ff.

(7) In the Cannizzaro reaction an aldehyde is oxidized to its corresponding acid (see page 491).

### REACTIONS OF MONOCARBOXYLIC ACIDS

The following summary of the reactions of the aromatic acids includes examples which are familiar from our study of the aliphatic series. This was to be expected, as we know that type groups preserve their individuality so far as possible. Whatever differences exist between aliphatic and aromatic acids are due to the influence of the aromatic ring, and the groups substituted upon it. For example, the table on page 540 shows that aromatic acids are stronger than those of the aliphatic series; their dissociation constants are affected by the nature and position of the groups on the ring.

(1) *Loss of carbon dioxide*; passage from acid to hydrocarbon. When its dry sodium salt is heated with excess of a strong base an aromatic acid loses carbon dioxide, producing an aromatic hydrocarbon:



This is analogous to the reaction by which methane is prepared from sodium acetate. The presence of a substituting group may aid in the decomposition (see salicylic acid, page 528).

(2) *Acid derivatives*. The acid chloride, amide, anhydride, and esters are formed in the same way as with any aliphatic acid. The following equations illustrate the formation of these derivatives from benzoic acid.

(a) *Acid chloride*.



Benzoyl chloride, whose formation is shown here, may also be made by special methods, as follows:

By Friedel and Crafts reaction (see equation, page 522).

By the action of chlorine upon benzaldehyde in the absence of catalysts (this is the **commercial method**):



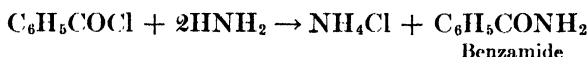
Benzoyl chloride may be taken as typical of aromatic acid chlorides. It is a liquid with an irritating, disagreeable odor, and is lacrymatory. The compound may be used as are aliphatic acid halides, to form any of the derivatives (esters, amides, etc.) which pertain to benzoic acid.

Benzoyl chloride is employed to ascertain the presence of OH or NH<sub>2</sub> groups in organic compounds. The derivatives formed in such instances are often solids capable of crystallization, while the use of acetyl chloride might yield liquids. As solids are more easily purified than liquids, and as

melting points are generally obtained with greater accuracy than are boiling points, one can see the advantages possessed by benzoyl chloride. To these must be added the fact that in its reactions it is apt to be a less violent reagent than acetyl chloride.

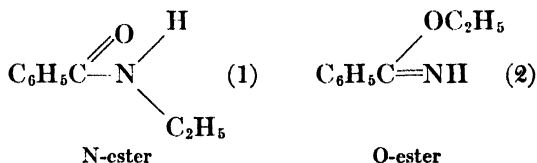
In esterification with benzoyl chloride the **Schotten-Baumann method** is generally employed. In using this method the alcoholic compound is treated with successive small portions of benzoyl chloride and ten per cent potassium hydroxide solution, or the reaction is carried out in pyridine solution. The alkali serves to hasten the reaction, and to neutralize the hydrochloric acid as it is formed; at the close of the reaction any excess acid chloride is decomposed and neutralized by the alkaline solution.

(b) *Amide*.

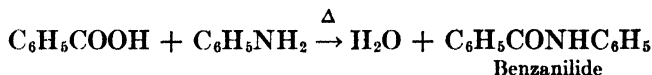


In the laboratory, benzamide is conveniently made from benzoyl chloride and ammonia water, or ammonium carbonate.

With benzamide we have another illustration of the tautomerism of amides, mentioned on page 229. Benzamide forms a silver salt which, when acted upon by ethyl iodide, yields its ethyl ester. This appears to have the structure shown at (2), since its hydrolysis gives benzoic acid, alcohol, and ammonia. The sodium salt of benzamide gives with ethyl iodide a compound having structure (1). This is shown by its hydrolysis, which gives benzoic acid and ethylamine.

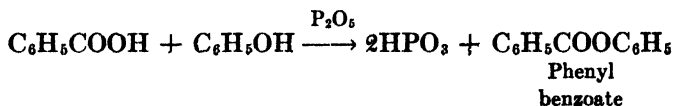
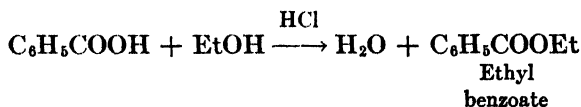


(c) *Anilide*.



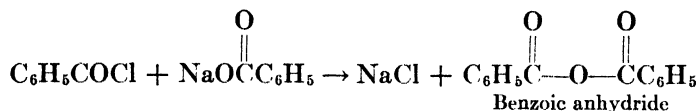
In addition to its preparation from benzoic acid, this compound results from benzophenone oxime through the Beckmann reaction (page 558)

(d) *Esters*.



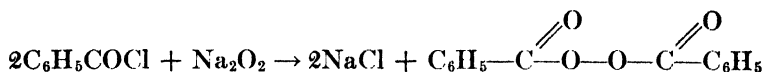
Esters may be made from benzoic acid by refluxing a mixture of the acid and alcohol, the mixture being first saturated with hydrogen chloride. The Schotten-Baumann reaction is also available. Ethyl benzoate has a characteristic odor, and is used in perfumes and flavors. Other alkyl esters have pleasant odors.

(e) *Acid anhydride.*



It goes without saying that any of these acid derivatives (amide, ester, anilide) might have been prepared either from benzoyl chloride or benzoic anhydride instead of from benzoic acid. (For use of benzoyl chloride in synthesis of acid chlorides, see page 188.)

(f) *Benzoyl Peroxide.* This compound is obtained by action of benzoyl chloride upon sodium peroxide:



The compound is fairly stable, but useful as an oxidizing agent (disinfectant). It is employed to bleach flour. By action of sodium ethoxide upon benzoyl peroxide, the sodium salt of perbenzoic acid is obtained:



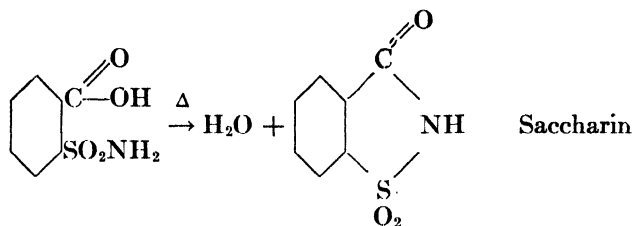
Free perbenzoic acid may be made from this salt. The acid is a good oxidizing agent.

#### SUBSTITUTION PRODUCTS OF BENZOIC ACID

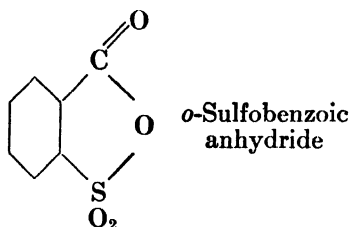
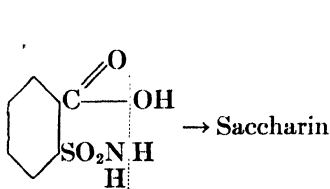
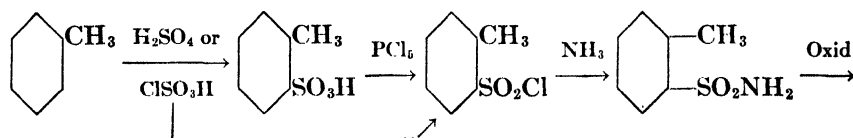
The acid derivatives of benzoic acid are like those of fatty acids, both in mode of formation, and in their general reactions. In the case of the substituted acids, whatever differences we find between the two series are caused by the benzene ring. The possibility of position isomerism is introduced in the aromatic substituted acids; likewise, as has been said, they are stronger acids than the fatty acids, by virtue of the presence of the phenyl group. In both groups, acid derivatives and substituted acids, are found compounds of considerable importance.

**Nitrobenzoic Acids.** Direct nitration of benzoic acid yields *m*-nitrobenzoic acid:



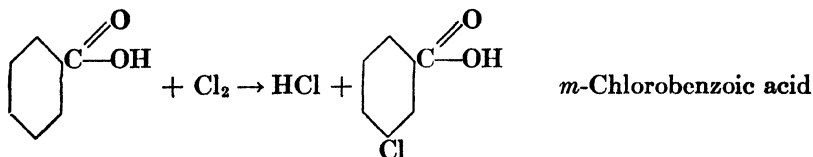


The compound which results, saccharin, is used as a sweetening agent, being many hundreds of times as sweet as cane sugar. Saccharin has no nutritive value and hence it may be used by diabetics, from whose dietary sugar has been removed. The sodium salt, which is much more soluble than saccharin, is often used in its place. Dulcin (page 511) is another compound, which like saccharin is many times sweeter than sugar. See also perilla oxime, page 763.

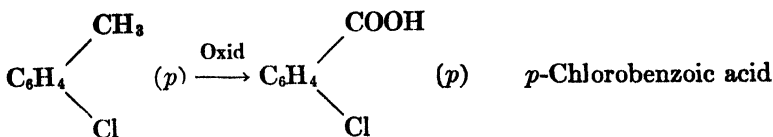


The anhydride of *o*-sulfobenzoic acid has reactions somewhat like those of phthalic anhydride, by which dye compounds are formed. Formulas are shown on page 690.

**Halogenated Benzoic Acids.** The *meta* derivative results from direct halogenation:



The *para* and *ortho* derivatives may, as usual, be obtained from oxidation of toluene compounds:



They are also obtained from the aminobenzoic acids through the diazotization reaction.

**Hydroxybenzoic Acids.** Of these the *ortho* acid leads in importance. *o*-Hydroxybenzoic acid (Salicylic acid) is obtained by heating sodium phenoxide with carbon dioxide under pressure. Sodium phenyl carbonate, the product of this reaction, rearranges into salicylic acid (salt). The equations will be found on page 500. Salicylic acid may also be made by a modification of the Reimer-Tiemann reaction (see Phenols, page 501).

Salicylic acid is a natural product found in fair amount in oil of winter-green as methyl salicylate, also in other natural sources. It is a colorless solid whose solubility in water, etc., is like that of benzoic acid. When slowly distilled, salicylic acid partially decomposes, yielding carbon dioxide and phenol;\* the presence of the OH group favors a more ready loss of carbon dioxide than is the case with benzoic acid, distillation with lime being necessary for this decomposition. Phenolic properties are also shown by the formation of a violet solution when salicylic acid is treated with ferric chloride reagent (see page 499). Salicylic acid is odorless, and it has powerful antiseptic properties. This leads to its substitution for phenol in certain instances. The acid and its salts have been used in the preservation of foods and in medicine. (See below.)

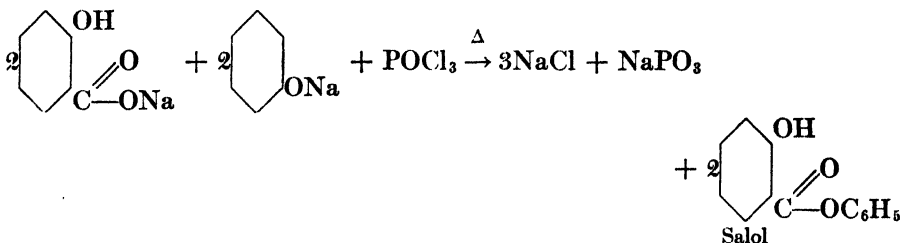
#### DERIVATIVES OF SALICYLIC ACID

**Aspirin** is acetylsalicylic acid. Like phenol, salicylic acid reacts with acetyl chloride or acetic anhydride. The derivative is a colorless solid.



Aspirin is used as an antipyretic, for headache, sore throat, neuralgia.†

**Salol** (phenyl salicylate) is used as an internal antiseptic.



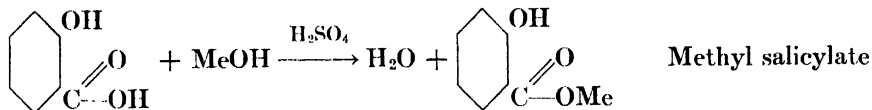
Salol is fairly stable to acid and is not hydrolyzed in the stomach. In the intestine hydrolysis takes place, liberating the two antiseptics, phenol and salicylic acid, so slowly that they cannot show toxic action. When a toxic substance is esterified as with salol and subsequently released by

\* Salol and xanthone are also produced.

† Over 6,000,000 pounds of aspirin were sold in this country in 1940.

hydrolysis, we have an example of the "salol principle." Both components may be active as with salol, or only one as with methyl salicylate. Salol can be used to coat pills which are to pass the stomach unchanged.

**Methyl salicylate** is the chief constituent of oil of wintergreen; it is used in medicine for rheumatism, and as an antiseptic. A more general use is for flavoring purposes. It may be synthesized as follows:



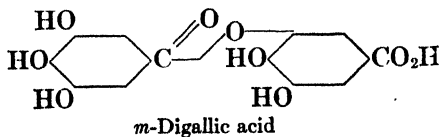
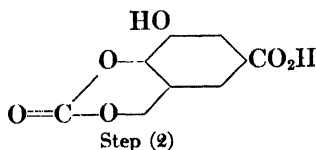
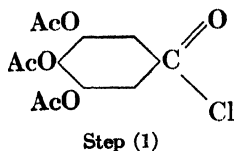
Isobutyl and isoamyl salicylates are used in perfumes and soaps to impart the odor of red clover.

**Additional Data.** When potassium phenoxide is heated to 150° in carbon dioxide, salicylic acid (salt) is formed, but at 220° the same reagents produce *p*-hydroxybenzoic acid. Likewise, potassium salicylate heated to 220° will rearrange to *p*-hydroxybenzoic acid. This acid is unlike salicylic acid in that it is non-volatile in steam, and gives a yellow precipitate with ferric chloride. Distillation yields carbon dioxide and phenol. Neither this acid nor the *m*-hydroxybenzoic acid has the antiseptic properties of salicylic acid.

#### OTHER HYDROXY ACIDS

**Gallic acid**,  $\text{C}_6\text{H}_2(\text{OH})_3\text{COOH}$  (3, 4, 5, 1) is an important polyhydroxy derivative of benzoic acid. This is found in many plants, in tea, walnuts, gall-nuts, and other sources. It is formed when tannin is treated with dilute acid. Heated, it loses carbon dioxide and yields pyrogallol. Ferric chloride gives a dark blue coloration and precipitate.

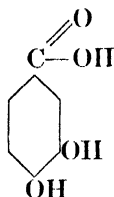
**Digallic acid**,  $\text{C}_{14}\text{H}_{10}\text{O}_9$ , a constituent of tannin, may be made from gallic acid by a series of steps which involve (1) protection of the hydroxyl groups of gallic acid and formation of the acid chloride, (2) protection of certain hydroxyl groups on the molecules to be esterified, (3) esterification, followed by hydrolysis to remove the protecting groups.



This substance belongs to the class called *depsides* which are esters formed between molecules of phenolic acids. It is a didepside.



**Protocatechuic acid**, like gallic acid, is a decomposition product of tannins, obtained from them as well as from various resins, such as asafœtida and myrrh, by fusion with potassium hydroxide. This acid when heated, loses carbon dioxide and passes to pyrocatechol. With ferric chloride, a green color is secured; ferrous salts give a violet color.



Protocatechuic  
acid

**Tannins**, or tannic acids, are substances commercially obtained from gall-nuts, hemlock or oak bark, or sumach, and from various other plants and trees, and applied to the tanning of leather,\* the mordanting of dyes and

TABLE 38.—PHYSICAL CONSTANTS OF AROMATIC ACIDS

Name	Formula	M.p., °C.	B.p., °C.	Ethyl ester, B.p., °C.	Amide, M.p., °C.
Benzoic.....	$C_6H_5CO_2H$	121.7	249.2	211.2	130
Toluic (o).....	$CH_3C_6H_4CO_2H$	104.5	259	227	147
Toluic (m).....		110-1	263	231 <sup>750</sup>	97
Toluic (p).....		179-80	274.5	235.5	165
Aminobenzoic (o).....	$NH_2C_6H_4CO_2H$	144-5	Sub.	266-8	108
Aminobenzoic (m).....		173-4		294	78-9
Aminobenzoic (p).....		187-8			182.9
Hydroxybenzoic (o).....	$HOOC_6H_4CO_2H$	159	Sub., 76	233-4	140
Hydroxybenzoic (m).....		201			170.5
Hydroxybenzoic (p).....		214.5			162
Chlorobenzoic (o).....	$ClC_6H_4CO_2H$	141-2			142.4
Chlorobenzoic (m).....		158			134.5
Chlorobenzoic (p).....		242-3	Sub.		178.3
Nitrobenzoic (o).....	$NO_2C_6H_4CO_2H$	147.5		149 <sup>10</sup>	176.6
Nitrobenzoic (m).....		140-1		298 ±	142-3
Nitrobenzoic (p).....		240-2	Sub.		200
Phthalic (o).....	$C_6H_4(CO_2H)_2$	206-8	Dec. >191	298-9	219-20 dec.
Phthalic (m).....		347.8	Sub.	302	
Phthalic (p).....		Sub. >300		302	
α-Naphthoic.....	$C_{10}H_7CO_2H$	160-1			202
β-Naphthoic.....		184	>300		192
1,8-Naphthalic.....	$C_{10}H_6(CO_2H)_2$	270			

\* Reaction of formaldehyde with aromatic phenols, sulfonic acids, or mixed derivatives yields compounds which have been applied to the tanning of leather under the trade name of Syntans.

the manufacture of writing ink. Tannins are water-soluble and possess an acid, astringent taste.

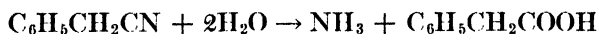
The reaction of tannins with gelatin, by which an insoluble mass is formed, is the basis of the process of converting hides to leather.\* Certain tannins give blue-black solutions with ferric chloride. If such a substance mixed with a ferrous salt is used in a writing ink, the oxidation of the ferrous salt to ferric will cause the writing to assume a dark color on the paper. An ink of this type may be reduced and rendered colorless by treatment with oxalic acid. Inks made from organic dye compounds do not usually suffer reduction by oxalic acid, but they are usually decolorized by a solution of sodium hypochlorite.

Tannins are substances of high molecular weight and apparently they possess structures of considerable complexity. In their decomposition by heat or hydrolysis, they yield, according to the conditions observed, gallic acid, pyrogallol, pyrocatechol, phloroglucinol, and other less familiar compounds. Certain of the tannins which yield glucose upon their hydrolysis appear to be esters of gallic acid or of digallic acid with the sugar.

In the study of such compounds Emil Fischer has prepared the penta-digalloyl ester of glucose, a compound whose molecular formula is  $C_{76}H_{52}O_{46}$ . This compound bears a close resemblance to natural Chinese tannin. Though the molecular weight is well over 1500 its structure is definitely known. In a continuation of this work Fischer prepared a giant molecule, again of known structure, whose molecular weight was 4021 and whose formula was  $C_{220}H_{142}N_4O_{53}I_2$ . Syntheses such as these give an indication of what success organic chemists may expect in their efforts to duplicate the more complex natural organic compounds.

#### SUBSTITUTED ALIPHATIC ACIDS

**Phenylacetic acid**,  $C_6H_5CH_2COOH$ , which is an isomer of the toluic acids, is a good example of a saturated phenyl fatty acid. It may be formed by the hydrolysis of benzyl cyanide:

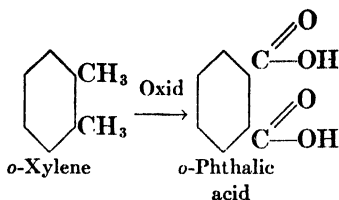


Its reactions resemble those of acetic acid. Upon oxidation, it reverts to benzoic acid. The toluic acids, on the contrary, are oxidized to benzene dicarboxylic acids (page 533). The esters of phenylacetic acid, and the acid as well, are used in perfumes; the acid is used in medicine as an antiseptic.

**Cinnamic acid**, whose synthesis from benzaldehyde is shown on page 551, is found in nature in oil of cinnamon and in Peru and Tolu balsams. This substance acts both as an acid and as an unsaturated compound, i.e., it

\* A weak solution of tannic acid was formerly used in the treatment of burns because of this hardening action.

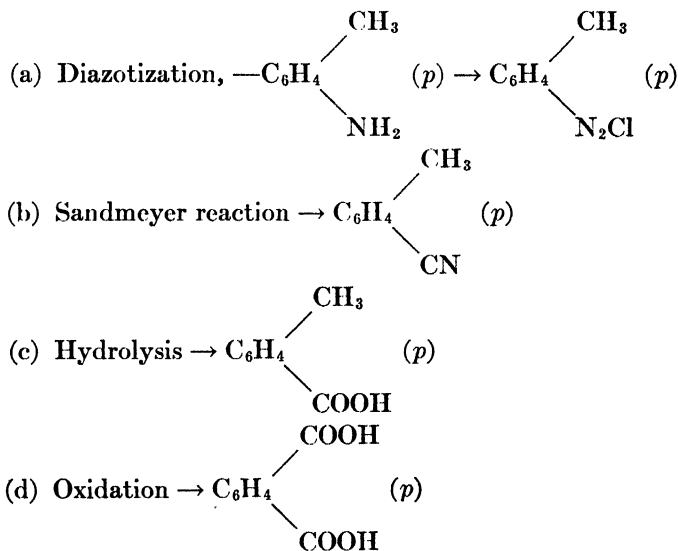




Commercially, the acid is produced from phthalic anhydride by hydrolysis.

(2) Isophthalic acid may be formed by the oxidation of *m*-xylene, also by the fusion of sodium formate with potassium *m*-sulfobenzoate (see example of this reaction on page 440), and by other methods.

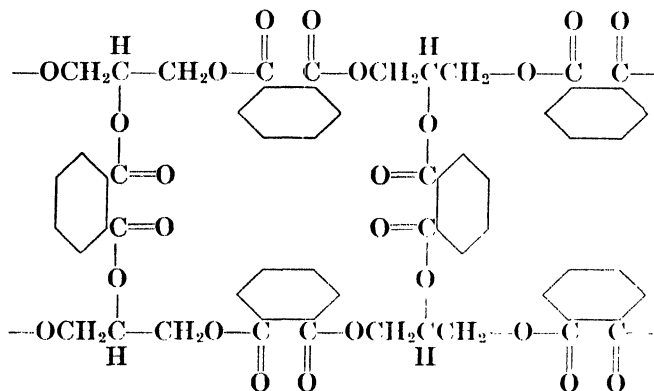
(3) Terephthalic acid results when *p*-dialkyl derivatives of benzene are oxidized. It may be formed from *p*-toluidine by the following steps:



The dicarboxylic acids of benzene furnish examples of all of the derivatives common to aliphatic dicarboxylic acids. Esters, normal and acid salts, amides, etc., are known.

**Uses of Phthalic Acid.** The potassium acid salt, which can be had in high purity, is used as a standard in acidimetry. Several esters are used in condensation pumps, in which a liquid with very low vapor pressure is essential (*n*-butyl, *n*-hexyl phthalates). Mercury, formerly used in this role, has been displaced by phthalates whose vapor pressure is less than that of mercury (di-2-ethylhexyl phthalate). Several are used as plasticizers for cellulose derivatives (dibutyl, diamyl, dimethyl, diethyl esters). Metallic phthalates have shown promise of usefulness in paints and lacquers. Esterification with glycerol gives mixtures of compounds of high molecular weight used as synthetic resins (Glyptals).

The following section of a formula shows how glycerol could be completely esterified with phthalic anhydride. The product of complete reaction would be brittle and not suited to the intended uses.



The resin is plasticized by introduction of an aliphatic acid to react with some of the hydroxyl groups of glycerol and prevent cross-linking. This "internal plasticizer" may be an unsaturated acid such as is furnished by linseed oil, and if so the resin will have air-drying properties (see page 217).

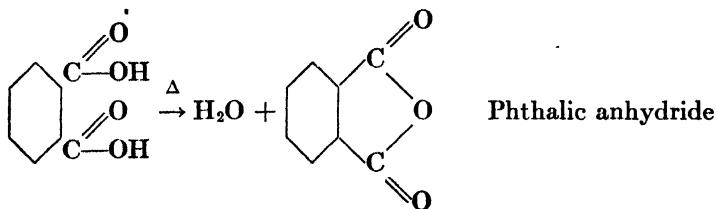
Paints made from these resins are used for traffic markers as they are water-resistant; the resins are used in printing inks, enamels, furniture finishes. They are very important for coating purposes due to their permanence and good appearance.

Chief use of phthalic anhydride is for glyptal production. Diethyl phthalate is a perfume material, also used to denature alcohol. Other uses for phthalic acid follow in the next section. For a chart of syntheses from phthalic anhydride, see Reference 10. United States production of phthalic acid and anhydride in 1940 was 58,000,000 pounds.

#### REACTIONS OF *o*-PHthalic ACID

The reactions of phthalic acid are important and interesting, and several of the reaction products have a prominent place in chemical practice.

(1) *Formation of anhydride.* It has been stated that phthalic acid loses water when heated, forming its anhydride:



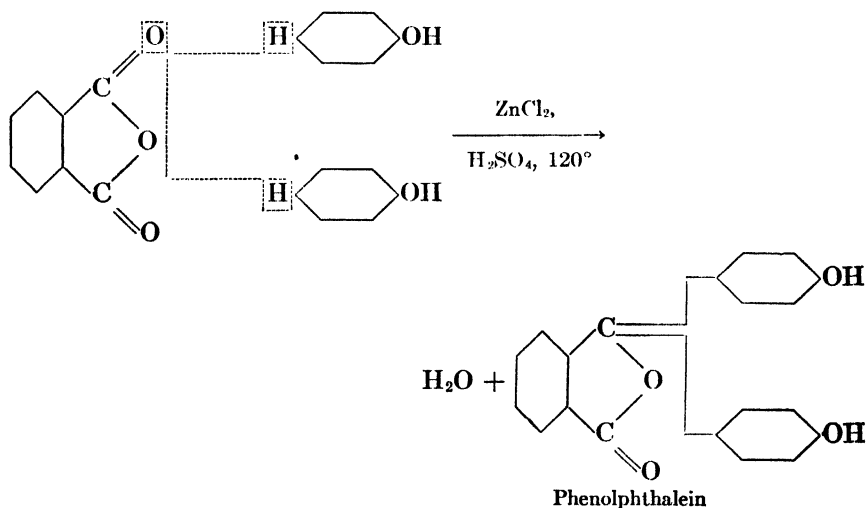
Neither *meta*- nor *p*-phthalic acid forms an anhydride, an explanation of which is suggested in the Baeyer strain theory discussed in Chapter XXXII.

Phthalic anhydride is **made commercially** from naphthalene by passing its vapor with air over a catalyst (vanadium oxide) heated to  $500^{\circ}$ . Another large-scale method formerly in use involved the oxidation of naphthalene with sulfuric acid in the presence of mercuric sulfate (catalyst).



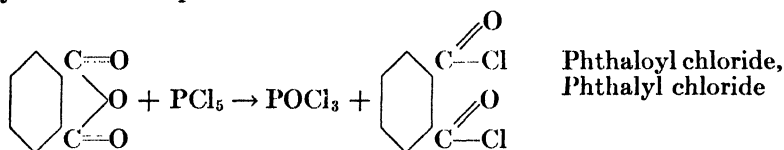
FIG. 84.—This acrylic denture, made of plastic based on Crystalite, can bite a pencil in half without damage to itself. (*Courtesy of Rohm and Haas Company.*)

One of the interesting reactions of phthalic anhydride is that which takes place with phenolic compounds. With these it forms derivatives called phthaleins. The reaction with phenol is typical:



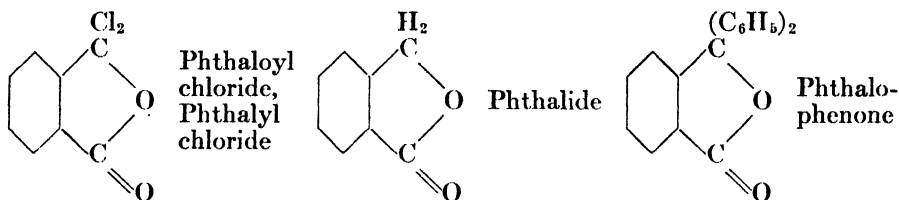
The *para* hydrogens of phenol together with carbonyl oxygen of the anhydride are removed as a molecule of water. Phenolphthalein, the product of this reaction, is a familiar indicator, much used in analytical chemistry. It is also of value in medicine as a laxative. An alkaline solution of phenolphthalein is a deep red color; other phthaleins likewise give colored alkaline solutions. They are discussed in the chapter on dyes.

(2) *Formation of acid chloride.* Treatment with phosphorus pentachloride converts phthalic acid to phthaloyl chloride; treatment of the anhydride is more practical:



Another method involves the reaction of phthalic anhydride and thionyl chloride, catalyzed by zinc chloride.

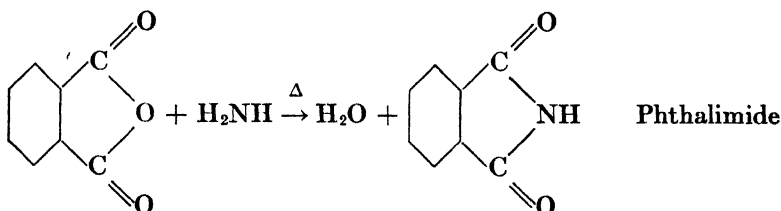
The compound exists in two forms, one of which has the formula shown above, while the other is a derivative of phthalic anhydride:



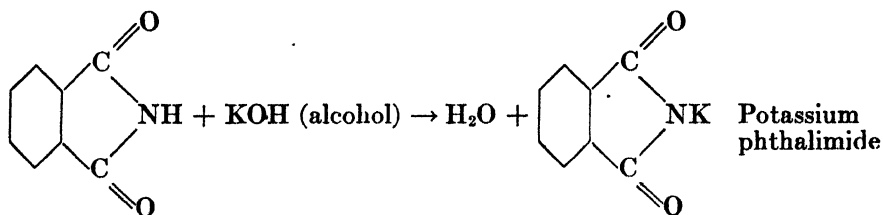
The symmetrical form changes to the unsymmetrical form when heated with aluminum chloride. Derivatives of both forms are known, but those of the unsymmetrical form are most important and most interesting. Two of these are phthalide and phthalophenone, whose formulas are shown here.

For use of phthaloyl chloride in synthesis of acid chlorides see page 188.

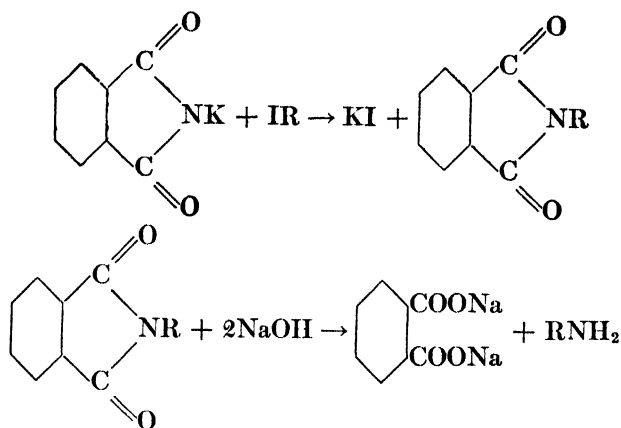
(3) *Phthalimide.* Ammonia reacts with phthalic anhydride forming phthalimide:



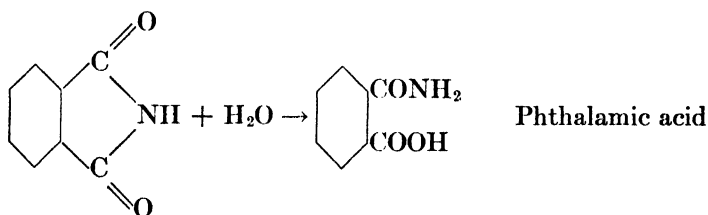
In this compound, the hydrogen lying between the two C=O groups is replaceable by a metal (note remarks on page 256), in this way giving a salt of the imide:



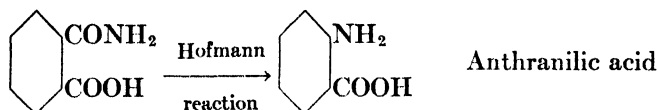
The salt is used in the **Gabriel Synthesis of Primary Amines** as diagrammed below:



The hydrolysis of phthalimide with barium hydroxide or ammonia yields phthalamic acid:



a compound which is employed in making anthranilic acid. Here we make use of the Hofmann reaction, in which an amine is produced when an amide with one more carbon atom is treated with a halogen in alkaline solution. Phthalamic acid treated with bleaching powder yields anthranilic acid:



or the latter may be made at one step from phthalimide by the use of the same reagents.

Phthalic acid may be converted to benzoic acid when heated with an equimolecular proportion of calcium hydroxide (see also page 521). An excess of this reagent carries the reaction a step further, yielding benzene and another molecule of carbon dioxide.

**Polycarboxylic Acids.** Derivatives of benzene with three, four, five, and six carboxyl groups are known. The last compound, called mellitic acid, exists as the aluminum salt in beds of lignite ("Honey Stone"). Mellitic acid,  $\text{C}_6(\text{COOH})_6$ , may be synthesized directly from charcoal or graphite by

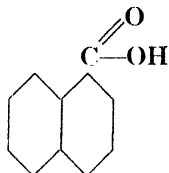


oxidation with potassium permanganate or nitric acid. The acid is resistant to the action of nitric or sulfuric acids, but yields carbon dioxide and benzene when its calcium salt is distilled.

### NAPHTHALENE CARBOXYLIC ACIDS

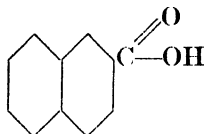
The monocarboxylic acids in this series are termed naphthoic acids. Methods of preparation are similar to those for benzoic acid.

$\alpha$ -Naphthoic acid is made from the hydrolysis of  $\alpha$ -naphthonitrile, or by treatment of  $\alpha$ -naphthalenesulfonic acid with sodium formate.



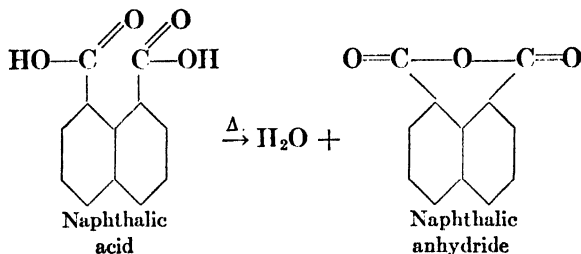
$\alpha$ -Naphthoic acid

$\beta$ -Naphthoic acid results from the hydrolysis of  $\beta$ -naphthonitrile or the oxidation of  $\beta$ -alkyl naphthalene compounds.



$\beta$ -Naphthoic acid

The reactions of these monoacids resemble those of benzoic acid. The diacids are similar to the phthalic acids. It is noteworthy that 1,8-naphthalic acid forms an anhydride on heating, as does *o*-phthalic acid:



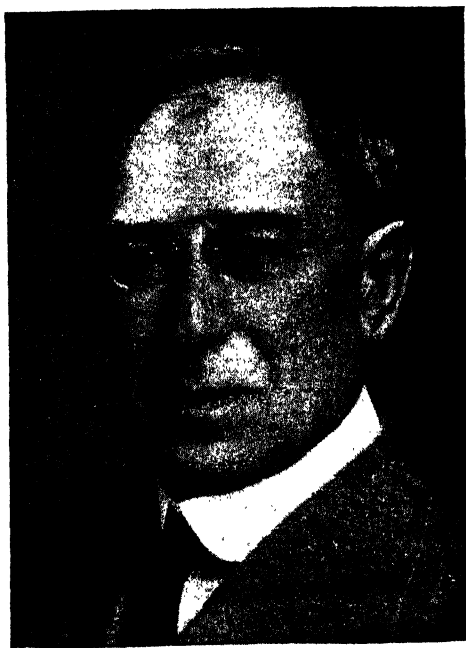
Naphthalic anhydride forms derivatives with phenols, which are similar in structure to the phthaleins formed from phthalic anhydride. Like phthalic anhydride it may be changed to an imide.

### STRENGTH OF ORGANIC ACIDS

In Table 39 the dissociation constants of benzoic acid and several of its substitution products are compared. The constants of formic and acetic acids are inserted to show the relative strength of the two series.

Inspection of this table will plainly show the effect of groups in the *ortho* position to carboxyl upon the dissociation constant of the acid. This

M. GOMBERG. (American, 1866-1947.) After preliminary schooling in America, Gomberg worked with Baeyer and with Victor Meyer. Here he made tetraphenylmethane, whose synthesis had been unsuccessfully attempted many times. Later work in America on synthesis of hexaphenylethane led to the discovery of triphenylmethyl. Gomberg was for many years professor of organic chemistry at the University of Michigan, the institution in which he did his own undergraduate work. See *Ind. Eng. Chem.*, **6**, 339 (1914), *ibid.*, **23**, 116 (1931); also this book, page 407.



V. N. IPATIEFF. (American, 1867- .) Ipatieff did much of his work in Russia; he came to America in 1931. His chief interest lies in high pressure catalytic reactions, in which field he has made notable contributions both to the theory and practice. The work is well described in his book, *Catalytic Reactions at High Pressures and Temperatures*, Macmillan, 1936; see *J. Chem. Education*, **14**, 553 (1937). See page 624, this book.

is particularly noticeable in the case of 2,6-dihydroxybenzoic acid, and in phthalic acid. Compare the effect of negative groups with that of alkyl group or amino group.

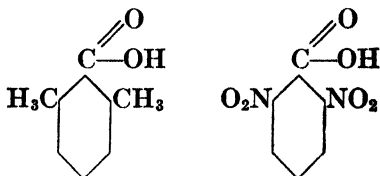
### STERIC HINDRANCE

In the case of certain derivatives of benzoic acid, great difficulty is experienced in carrying out reactions which apparently should be normal for the compound. This happens when groups are substituted in both positions *ortho* to the carboxyl group.

TABLE 39.—DISSOCIATION CONSTANTS OF AROMATIC ACIDS

	T = 25°C.	100 × K
Formic.....		0.01712
Acetic.....		0.00175
Benzoic.....		0.0063
<i>o</i> -Nitrobenzoic.....		0.671
<i>m</i> -Nitrobenzoic.....		0.0321
<i>p</i> -Nitrobenzoic.....		0.0376
<i>o</i> -Chlorobenzoic.....		0.120
<i>m</i> -Chlorobenzoic.....		0.0148
<i>p</i> -Chlorobenzoic.....		0.0104
<i>o</i> -Hydroxybenzoic.....		0.105
<i>m</i> -Hydroxybenzoic.....		0.0083
<i>p</i> -Hydroxybenzoic.....		0.0029
Dihydroxybenzoic (2,6).....		5.00
Dihydroxybenzoic (2,3).....		0.114
Dihydroxybenzoic (2,5).....		0.108
Dihydroxybenzoic (2,4).....		0.0505
Phthalic.....		0.117 = K <sub>1</sub>
Isophthalic.....		0.029 = K <sub>1</sub>
Terephthalic.....		0.015 = K <sub>1</sub>
<i>o</i> -Toluic.....		0.0123
<i>m</i> -Toluic.....		0.00535
<i>p</i> -Toluic.....		0.00424
<i>o</i> -Aminobenzoic.....		0.00107
<i>m</i> -Aminobenzoic.....		0.00163
<i>p</i> -Aminobenzoic.....		0.00121

Examples:



Neither of the above compounds forms an ester when boiled with alcohol in the presence of hydrogen chloride, a method which is effective with most aromatic acids. The esters are, however, obtained from the action of alkyl halides upon the silver salts of these acids; thus the acids are shown to be capable of esterification.

The theory of Victor Meyer states that the tardiness of reaction of compounds similar to these is due to a crowding caused by the close proximity of the three groups on the ring, which interferes with the close approach of a fourth group. The phenomenon is termed *steric hindrance*. It is significant that the esters, once formed, resist hydrolysis, as do other di-*ortho* derivatives

of  $\text{C}_6\text{H}_5\text{C}(=\text{O})\text{OH}$ ,  $\text{C}_6\text{H}_5\text{CN}$ ,  $\text{C}_6\text{H}_5\text{C}(=\text{O})\text{NH}_2$  . . . , etc.

We have noted a similar phenomenon with the substituted biphenyls (page 421). Many other examples both for aliphatic and aromatic compounds are found in the literature. For instance, both trichloroacetic and trimethylacetic acids have lower esterification rate than acetic acid. The factor of most importance in steric hindrance appears to be the size of the groups involved, but there are other factors. Like many other subjects encountered in our work, it will need more research for complete elucidation.

### REVIEW QUESTIONS

- Write graphic formulas for: (a) Phthalide; (b) Terephthalic acid; (c) Benzoyl bromide; (d) Phenylacetonitrile; (e) Phthaloyl chloride; (f) *m*-Cyanobenzenesulfonic acid.
- Give the formulas of two hydrocarbons, two ketones, and two alcohols, which upon oxidation would yield benzoic acid.
- Show the formation of benzoic acid from the following compounds: (a) Aniline; (b) Benzenesulfonic acid; (c) Chlorobenzene; (d) Benzene.
- How may the following changes be brought about: (a) *p*-Xylene to *p*-toluic acid? (b) *o*-Toluic acid to toluene? (c) Aniline to benzamide?
- Indicate by means of equations how the following exchanges may be made on the benzene nucleus:  
(a) H for  $\text{CO}_2\text{H}$ ; (b)  $\text{CO}_2\text{H}$  for H; (c) H for  $\text{NH}_2$ ; (d)  $\text{NH}_2$  for H; (e) CN for  $\text{NO}_2$ ; (f) H for  $\text{CH}_2\text{—CH}_2\text{—CH(OH)—CO—NH}_2$ .
- How could phenol and benzoic acid be distinguished from each other?
- List four compounds derived from benzoic acid which have practical uses. Give synthesis of each and state uses of the compound.
- Show by equations a method of synthesis for each of the phthalic acids.
- Show by means of equations the synthesis of the following compounds from phthalic anhydride: (a) Anthranilic acid; (b) Benzene.
- An aromatic hydrocarbon of formula  $\text{C}_8\text{H}_{10}$  gives upon oxidation, a substance of formula  $\text{C}_7\text{H}_6\text{O}_2$ . Another hydrocarbon of the same formula gives after oxidation the compound  $\text{C}_8\text{H}_6\text{O}_4$ . Write structures of the hydrocarbons and of their oxidation products.
- Write equations for the synthesis of benzoyl chloride and for three reactions of the compound.
- How could  $\text{C}_6\text{H}_5\text{COCl}$  and  $\text{C}_6\text{H}_5\text{CH}_2\text{Cl}$  be distinguished from one another? Describe the tests briefly.
- How could  $\text{C}_6\text{H}_4(\text{CH}_3)\text{COOH}$  be distinguished from  $\text{C}_6\text{H}_5\text{CH}_2\text{COOH}$ ? Describe the tests briefly.
- (R)14. Suggest how you would make phenylacetic acid from benzene.
- (R)15. How might phenylpropionic acid be made from benzene?
16. Define the phenomenon called "steric hindrance." How is it explained?

17. Show by sequences of equations how to make salicylic acid from *o*-sulfobenzoic acid; from anthranilic acid.
18. Show by a sequence of equations how to make *m*-chlorobenzamide from *m*-nitrotoluene.
19. Show how to make *o*-, *m*-, and *p*-bromobenzoic acids from benzene.
20. Make a chart showing the chemical interrelationships of benzoic acid, benzamide, ethyl benzoate, benzenesulfonic acid, aniline, *m*-nitrobenzoic acid.
21. What would be formed from *p*-toluic acid upon treatment with: (a) Chlorine (with a carrier); (b) Sodium hydroxide; (c)  $\text{PCl}_5$ ? Show how *o*-toluic acid would react with the same reagents.
22. Enumerate the methods given in this chapter for the preparation of  $\text{C}_6\text{H}_5\text{COOH}$  and similar acids. Which of these methods could be used to make acetic acid?
23. Indicate by a series of equations how benzamide might be transformed to other intermediate compounds and again to benzamide by the use of the Hofmann reaction, Sandmeyer reaction, etc.
24. List the compounds taken up in this chapter which are used in perfumes. Make a separate list of those with antiseptic value, and another list of those used to make dyes.
25. What is the "salol principle"? To what type of compounds is it applied?
26. How many cc. of  $\text{N}/10$   $\text{KOH}$  solution would be neutralized by 0.8056 g. of potassium hydrogen phthalate?
27. Cite the chemical reactions used in this chapter which bear the names of chemists. Give an equation for the employment of each of these reactions.
28. Write the graphic formula for the pentadigalloyl ester of glucose. (Use the open-chain aldehyde form of glucose.)
29. Phthalide is a lactone or internal ester. From what acid is this lactone formed? Write its formula and name it.
30. Suggest how to make the acid considered in question 29 from benzene.
31. How could *o*-nitrobenzoic acid be made from the aromatic nitro compound of formula  $\text{C}_7\text{H}_7\text{NO}_2$ ?
32. How could a mixture of benzoic acid, phenol, and *p*-dichlorobenzene be separated?
33. How has it been shown that benzamide can have two structures?
34. If aspirin were contaminated with salicylic acid what tests would reveal this fact?
35. What physical and chemical facts are of use in the identification of an aromatic acid such as benzoic acid? What derivative may be used to close the identification?
36. Discuss the isomerism shown by cinnamic acid. Write equations for the action of cinnamic acid with: (a) Oxidizing agents; (b) A halogen; (c)  $\text{HBr}$ .
37. What is the Schotten-Baumann reaction? What compounds would be formed in that type of reaction between benzoyl chloride and: (a) *o*-Toluidine; (b) *n*-Propyl alcohol; (c) Diethylamine?
38. Combustion of a 0.150 g. sample of the compound (A) gives 0.4437 g. of  $\text{CO}_2$  and 0.0794 g. of  $\text{H}_2\text{O}$ . The compound was boiled with  $\text{NaOH}$  solution for some time and the mixture was then acidified. Two compounds, (B) and (C) were isolated. (B) contains 72.97% C, 5.41% H. It can be made from benzaldehyde and acetic anhydride by the Perkin reaction. (C) contains 77.8% C and 7.41% H. It reacts with metallic sodium, liberating hydrogen, but it does not reduce Fehling solution. Mild oxidation produces benzaldehyde and vigorous oxidation gives benzoic acid. What is the structure of (A)?
39. An organic compound (A) contains 80.0% C, 6.67% H, and 13.33% O. It is oxidized by ammoniacal silver nitrate solution and forms a solid compound when treated with sodium bisulfite solution. Vigorous oxidation yields a compound (B) containing 57.84% C, 3.62% H, and 38.55% O. When (B) is strongly heated, it passes to a new compound (C) containing 64.87% C, 2.70% H, and 32.43% O (m.p.,  $129 \pm 1^\circ\text{C}$ ). Treatment of (A) with cold concentrated  $\text{KOH}$  solution gives two compounds, (D) and (E). (D) is an acid whose sodium salt contains 14.55% Na. (D) may be made from (A) by careful oxidation. (E) reacts with metallic sodium, and with acetyl

chloride, but does not reduce Fehling solution. (E) may be made from (A) by careful reduction. Deduce the structure of (A) and explain all of the reactions referred to here.

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# CHAPTER XXVIII

## AROMATIC ALDEHYDES, KETONES, AND QUINONES

### AROMATIC ALDEHYDES

Aromatic aldehydes have the type group, CHO, attached either to a nucleus such as the benzene ring, or to the side-chain on a ring. Those which belong to the latter class are unimportant for our discussion, and will not require detailed description. They are prepared like aliphatic aldehydes and they undergo quite similar chemical transformations. Aromatic and aliphatic aldehydes are not to be so sharply differentiated from each other as was possible in the case of phenols and alcohols, or aliphatic and aromatic amines. Both series participate in a large number of reactions, however it may be said that the aromatic aldehydes present the greater

TABLE 40.—PHYSICAL CONSTANTS OF ALDEHYDES AND KETONES

Name	Formula	M.p., °C.	B.p., °C.	Sp. g., 20°/4°	Oxime, M.p., °C.	Phenyl- hydra- zone, M.p., °C.
Benzaldehyde.....	$C_6H_5CHO$	— 26	179	1.046	128–30	155–6
Toluic aldehyde ( <i>o</i> ).....	$CH_3C_6H_4CHO$	.....	196–9	1.039	49	105–6
Toluic aldehyde ( <i>m</i> ).....	.....	.....	199	1.019	60	90
Toluic aldehyde ( <i>p</i> ).....	.....	.....	204–5	.....	(79)(110)	121
Hydroxybenzaldehyde ( <i>o</i> ).....	$HOC_6H_4CHO$	— 7	196.5	1.153 <sup>25</sup>	57	142–3
Hydroxybenzaldehyde ( <i>m</i> ).....	.....	106–8	240 ±	.....	87–8	130
Hydroxybenzaldehyde ( <i>p</i> ).....	.....	116–7	Sub.	1.129 <sup>130</sup>	72–3	177
Chlorobenzaldehyde ( <i>o</i> ).....	$ClC_6H_4CHO$	11	208 <sup>748</sup>	1.29 <sup>8</sup>	75–6	86
Chlorobenzaldehyde ( <i>m</i> ).....	.....	17–8	213–4	1.250 <sup>15</sup>	70–1	134
Chlorobenzaldehyde ( <i>p</i> ).....	.....	47.8	213 <sup>748</sup>	1.196 <sup>61</sup>	106	127
Nitrobenzaldehyde ( <i>o</i> ).....	$NO_2C_6H_4CHO$	40.9	153 <sup>25</sup>	.....	102–3	156
Nitrobenzaldehyde ( <i>m</i> ).....	.....	58	164 <sup>23</sup>	.....	121–3	120
Nitrobenzaldehyde ( <i>p</i> ).....	.....	106.5	Sub.	.....	129	153–4
Naphthaldehyde ( $\alpha$ ).....	$C_{10}H_7CHO$	33–4	291.6	1.148	98(39)	80
Naphthaldehyde ( $\beta$ ).....	.....	60.5	.....	1.078 <sup>99</sup>	.....	206 Dec.
Phenylacetaldehyde.....	$C_6H_5CH_2CHO$	33–4	193–4	1.025	98.5	62–3
Cinnamic aldehyde.....	$C_6H_5-\overset{H}{\underset{H}{C}}=C-CHO$	— 7.5	252 ±	1.110 <sup>20/20</sup>	138.5	168
Acetophenone.....	$CH_3COC_6H_5$	20.5	202 <sup>740</sup>	1.033 <sup>15/15</sup>	59	105–6
Benzophenone.....	$C_6H_5COC_6H_5$	48.5	305.4	1.083 <sup>54</sup>	143–4	197–8
		( $\alpha$ )		( $\alpha$ )		

number of reactions of specific interest. Those differences in chemical properties which set the two series apart will be emphasized as we proceed.

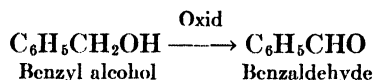
**Physical Properties.** Benzaldehyde or oil of bitter almonds,  $C_6H_5CHO$ , is a typical aromatic aldehyde. This substance is a colorless oil, insoluble in

water, but soluble in alcohol, ether, etc. Its odor is like that of bitter almonds. Other aromatic aldehydes are liquids or solids, generally possessed of pleasant odors.

### PREPARATION

The following methods are available for the preparation of the aromatic aldehydes.

- (1) The oxidation of a primary aromatic alcohol:



This method of preparation, which is so commonly used for aliphatic aldehydes, has much less significance in the aromatic series. Aliphatic alcohols are available in large quantities and form a natural starting point in the synthesis of compounds of that series, while in the aromatic series the hydrocarbons are the chief originals. Thus benzaldehyde is prepared from toluene or its derivatives.

(2) Production directly from toluene: (a) Étard method. Toluene dissolved in carbon disulfide may be oxidized with chromyl chloride. A precipitate is produced, consisting of the hydrocarbon combined with the reagent. Treatment of this precipitate with water yields benzaldehyde. This method of synthesis is applicable for the preparation of benzaldehyde derivatives as well. (b) Toluene may be directly oxidized to benzaldehyde by air in presence of a catalyst, or (c) by the use of manganese dioxide and sulfuric acid at 40°. Benzaldehyde made from benzyl or benzylidene chloride may have with it a small amount of material with chlorine in the ring. This would be unsuitable for use in perfume, hence methods like the above which avoid chlorination have distinct value.

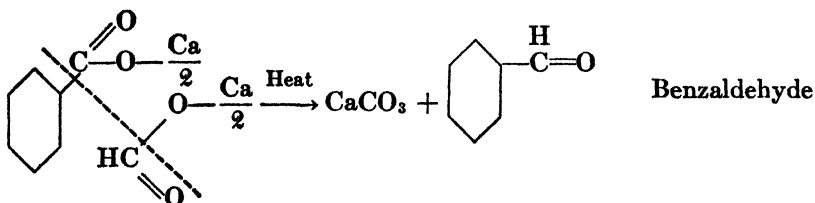
- (3) Indirect production from toluene.

(a) Toluene is transformed to benzylidene chloride (page 431) which upon hydrolysis gives benzaldehyde.

(b) Benzyl chloride derived from toluene (page 431) is oxidized by lead nitrate or copper nitrate in aqueous solution:



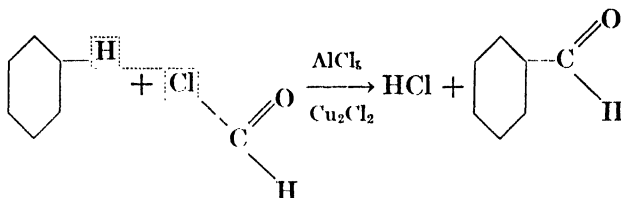
(4) Aromatic aldehydes are formed (usually in very low yield) by heating the calcium salts of aromatic acids with calcium formate:



This reaction has its identical counterpart in the aliphatic series.



(5) Benzaldehyde and other aromatic aldehydes may be formed directly from hydrocarbons by the combined reaction of carbon monoxide and hydrogen chloride, in the presence of aluminum chloride and cuprous chloride used as catalysts. (Gattermann reaction.) It seems likely that the carbon monoxide and hydrogen chloride exist in part as formyl chloride, which is able to react with the hydrocarbon as other acid chlorides do:

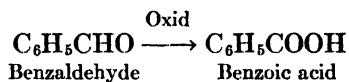


The Friedel and Crafts reaction taken up in Chapter XXIX is similar to the above.

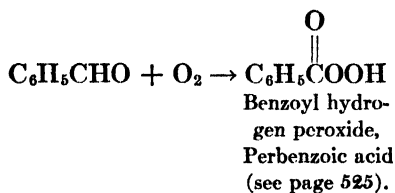
Benzaldehyde may be obtained from the glucoside amygdalin, a component of bitter almonds. When amygdalin is boiled with a dilute acid it is hydrolyzed; glucose, hydrogen cyanide, and benzaldehyde are its cleavage products. Hydrolysis may also be brought about by grinding the almonds with water, being caused in this instance by a natural ferment or enzyme called emulsin, which accompanies the amygdalin in the almond.

#### CHEMICAL REACTIONS

(1) *Oxidation.* Aromatic aldehydes are quite susceptible to oxidation, passing to their corresponding acids:



Benzaldehyde is oxidized by exposure to air; this accounts for the deposit of crystals often seen about the cork of a bottle, when it has become saturated with the oil. The oxidation by air proceeds in stages. First we have the addition of a molecule of oxygen to benzaldehyde, by which benzoyl hydrogen peroxide is formed:



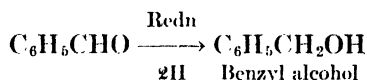
The peroxide compound is able to oxidize another molecule of aldehyde:



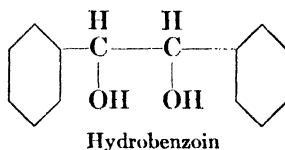
It may be remarked in passing that this reaction of benzaldehyde with oxygen (auto-oxidation) is not unique. A number of substances appear to be oxidized by oxygen through a similar mechanism, viz., the addition of oxygen to the compound, yielding a peroxide, which then performs the oxidation of unattacked material by giving up a portion of its oxygen.\* The air oxidation of aldehydes may be prevented by the use of an antioxidant (an easily oxidized organic or inorganic substance) in low concentration. Auto-oxidation may be desirable, and can in some cases be hastened by the use of a promoter. See "auto-oxidation of oils," page 217.

Benzaldehyde and its homologs reduce ammoniacal silver solutions; however Fehling's solution is not reduced by benzaldehyde. The Schiff test is positive.

(2) *Reduction.* Benzaldehyde upon reduction yields benzyl alcohol:



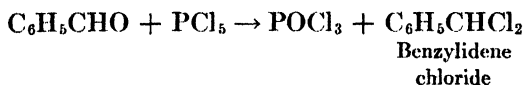
At the same time some of the compound hydrobenzoin is formed, through union of two partly reduced molecules of aldehyde:



This reaction is suggestive of the formation of pinacols by the reduction of ketones (page 154) but it is not shared by the aliphatic aldehydes.

(3) *Action of halogens.* Halogens interact with aromatic aldehydes by substitution. The hydrogen of the aldehyde group is replaced by halogen atom, giving as a final product an aromatic acid halide (for equation see page 523). Benzoyl chloride, which is a synthetic agent of some importance, may be produced on a commercial scale in this way. It will be recalled that when halogens react with aliphatic aldehydes the hydrogen atoms of their alkyl groups are replaced (page 144). In benzaldehyde there is no alkyl hydrogen.

(4) *Reaction with phosphorus pentachloride.* Aromatic and aliphatic aldehydes react alike with phosphorus pentachloride, i.e., aldehyde oxygen is replaced by two chlorine atoms:

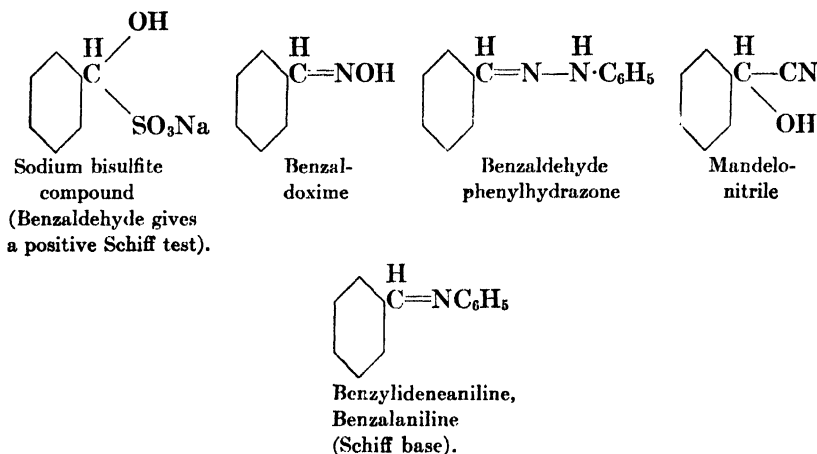


\* The peroxide may oxidize some compound other than the original aldehyde; thus a substance not directly oxidizable by oxygen may be oxidized in the presence of a compound capable of auto-oxidation (capable of forming a peroxide).

(5) *Behavior toward alkali.* The lower aliphatic aldehydes (with exception of formaldehyde) undergo condensation or are polymerized by the action of strong alkali. Aromatic aldehydes (and formaldehyde) in contact with alkali undergo simultaneous oxidation and reduction (the Cannizzaro reaction). (See equation, page 491.) One molecule of aldehyde is oxidized at the expense of another which is thereby reduced.

Formaldehyde resembles benzaldehyde in that neither has *alpha* hydrogen. The ordinary type of condensation is barred for this reason. The Cannizzaro reaction is catalyzed by peroxides and in their absence it does not occur. Very probably we will never fully realize the importance of such "impurities" in directing the course of chemical reactions.

(6) *Addition reactions and simple condensations.* Aromatic aldehydes resemble their aliphatic congeners in that they perform additions or condensations with sodium bisulfite, hydroxylamine, phenylhydrazine, hydrogen cyanide, and primary amines. The structures of the derivatives formed from benzaldehyde with these reagents are:



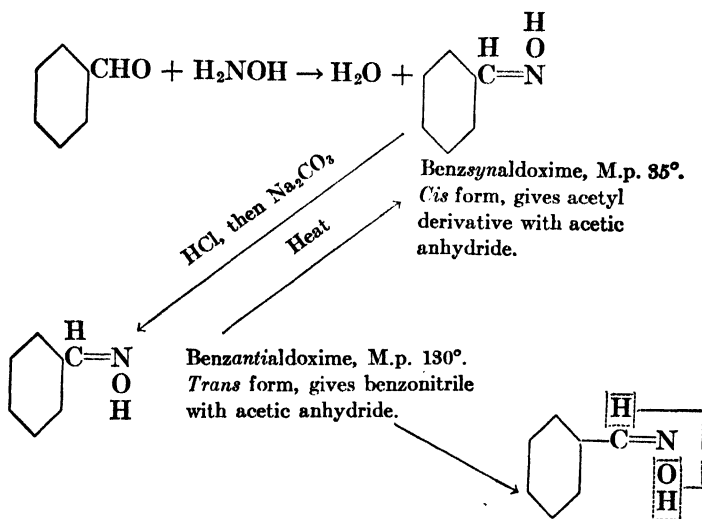
The bisulfite compounds of the aldehydes are solids. The formation of a bisulfite compound during the purification of an aldehyde is a handy means of removing the latter from a mixture. Subsequent treatment with dilute acid regenerates the pure aldehyde from the bisulfite compound.

Phenylhydrazones are used in the aromatic series to aid in the identification of aldehydes. They are solids which may be recrystallized, and whose melting points may be accurately determined. If the boiling point of the aldehyde and the melting point of its phenylhydrazone both agree with the tabular values, the identity of the aldehyde may be considered as proved (page 769).

The action of hydroxylamine with benzaldehyde produces an oxime (see above) whose melting point is 35°. If this oxime is treated with hydrochloric or sulfuric acid, it passes into another compound with identical

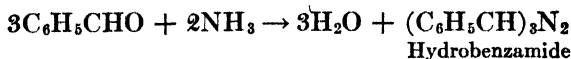
molecular formula, but with a melting point of  $130^{\circ}$ . The reverse change may be brought about by distillation at reduced pressure. These two compounds are thought to be geometrical or *cis-trans* isomers, one of the other (see pages 59 and 328). Treatment with acetic anhydride serves to distinguish their structures. Thus the compound of melting point  $35^{\circ}$  forms an acetyl derivative with this reagent, while its isomer loses water, forming a nitrile.

The latter has up to recent years been assumed to have the *cis* structure, since it was thought that H and OH would be more easily removed from such a compound. The idea, though simple and attractive, has been abandoned in favor of the *trans*-elimination idea. The facts presented are summarized below:



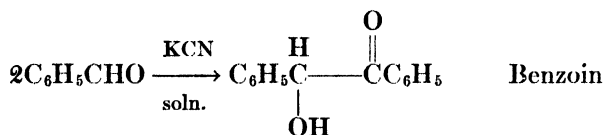
The *anti* oxime is formed from the *syn* compound by first making a salt with hydrochloric or sulfuric acid, then neutralizing the acid with sodium carbonate. The *syn* oxime reforms from the *anti* after continued heating at reduced pressure.

(7) *Action of ammonia.* Aliphatic aldehydes form addition compounds with ammonia. The aromatic undoubtedly do so as well, but the reaction proceeds beyond the first step and becomes complex.



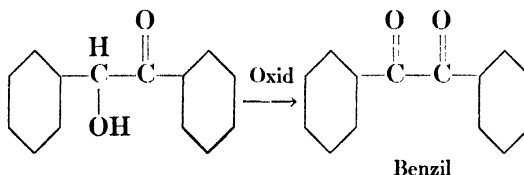
#### (8) Condensation Reactions.

(a) *Benzoin condensation.* Benzaldehyde condenses with itself when treated with a solution of potassium cyanide. The reaction, which is in some respects similar to the aldol condensation, is known as the benzoin condensation:

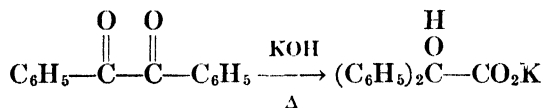


Other aromatic aldehydes react similarly in the presence of potassium cyanide solution.

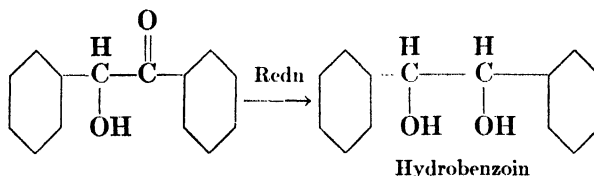
Benzoin is a derivative of the hydrocarbon bibenzyl,  $\text{C}_6\text{H}_5\text{CH}_2\text{—CH}_2\text{C}_6\text{H}_5$ , to which it may be transformed by reduction. Oxidized with nitric acid, benzoin yields the diketone benzil:



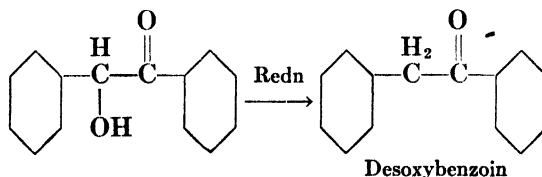
When benzil is heated with alcoholic potassium hydroxide solution it undergoes the benzilic acid rearrangement, giving potassium benzilate:



Benzoin reduced with sodium amalgam passes to hydrobenzoin:



a glycol derivative; whereas reduction with zinc and hydrochloric acid affects the alcohol group, giving desoxybenzoin:



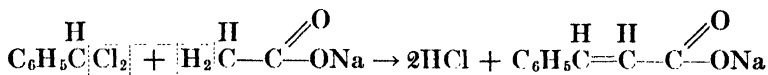
As a ketone-alcohol, benzoin somewhat resembles the simple sugars. It reduces Fehling's solution, also forms a phenylhydrazone and osazone. As a ketone it forms oximes.

(b) *Perkin reaction.* When benzaldehyde is treated with acetic anhydride and sodium acetate a condensation ensues between the aldehyde and the

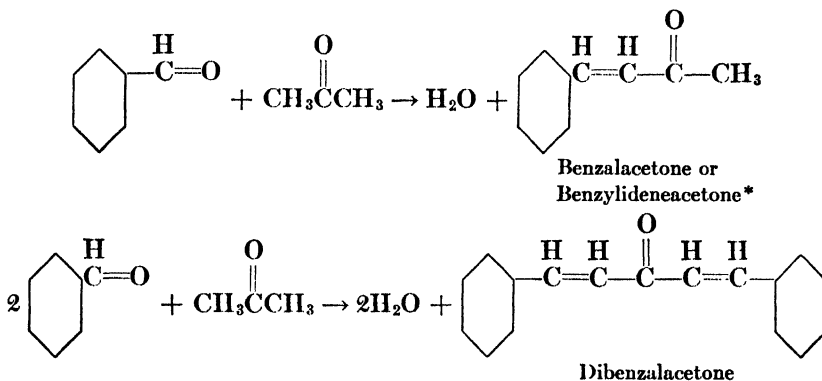
anhydride. Formulas of hypothetical intermediate compounds are:  $\text{C}_6\text{H}_5\text{-CHOHCH}_2\text{CO}\cdot\text{O}\cdot\text{COCH}_3$ , and  $\text{C}_6\text{H}_5\text{CH=CHCO}\cdot\text{O}\cdot\text{COCH}_3$ . The final product is cinnamic acid,  $\text{C}_6\text{H}_5\text{CH=CHCOOH}$ .

This condensation, known as the Perkin reaction, may be used to form a large number of benzene derivatives by varying the aldehyde and other reagents employed.

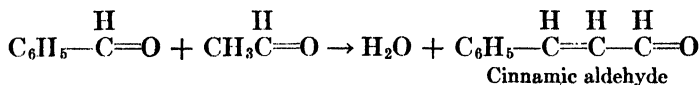
Cinnamic acid may be more cheaply synthesized from benzylidene chloride and sodium acetate:



(c) *Other aldol condensations.* In the presence of mild alkali, benzaldehyde and other aromatic aldehydes react with aliphatic aldehydes and ketones by aldol condensation. The number of applications of this reaction is naturally very large. A few examples are appended:

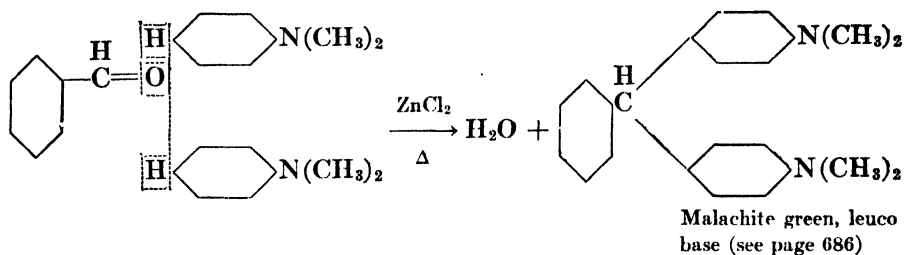


Dibenzalacetone is a convenient derivative for the identification of either benzaldehyde or acetone.

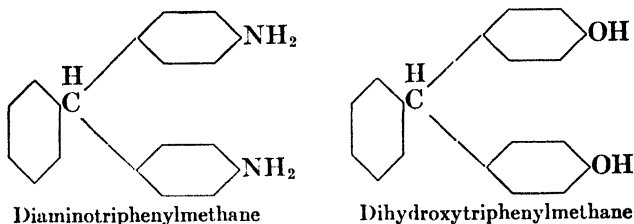


(d) *Further condensations.* In the discussion of phenol, aniline, and derivatives, it was shown that the *para* hydrogen atom of such compounds is easily removed or replaced. This is especially the case with tertiary amines of the type of dimethylaniline (page 472). Making use of this peculiarity, very important dye substances may be formed by interaction of these compounds with benzaldehyde. An example of such a dye is malachite green, made from dimethylaniline and benzaldehyde:

\* The reaction of benzalacetone with sodium hypochlorite is interesting. Chloroform and cinnamic acid are formed.



Other compounds which may be made in this way include diaminotriphenylmethane and dihydroxytriphenylmethane:



(9) *Action of acids upon benzaldehyde.* Nitric acid acts by substitution and not as an oxidizing agent. *m*-Nitrobenzaldehyde results. With sulfuric acid, benzaldehyde forms *m*-sulfobenzaldehyde.

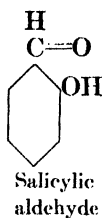
**Comparison of Aromatic and Aliphatic Aldehydes.** Benzaldehyde differs from aliphatic aldehydes in its reaction with strong bases (does not form a resin), with ammonia, with potassium cyanide, and with Fehling's solution. Reactions in which aliphatic aldehydes and benzaldehyde act similarly are oxidation, addition of sodium bisulfite (hydroxylamine, phenylhydrazine), and the aldol condensation (when benzaldehyde reacts with aliphatic compounds and not with itself).

### IMPORTANT AROMATIC ALDEHYDES

Benzaldehyde, which has been discussed at some length, is an important reagent. Certain dyes are made from it, also compounds of importance, as cinnamic acid, cinnamic aldehyde, etc., as has been illustrated. Its pleasant odor renders it desirable for perfumes.

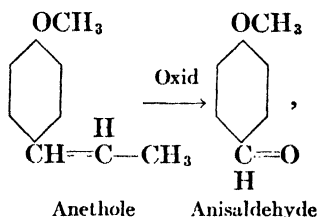
**Cinnamic aldehyde**, the odorous component of oil of cinnamon, may be obtained from that source by shaking the oil with concentrated sodium bisulfite solution. The precipitate of aldehyde bisulfite compound is then decomposed with sodium carbonate. For synthesis from benzaldehyde, see p. 551.

**Salicylic aldehyde** may be formed by the oxidation of saligenin,  $C_6H_5(OH)(CH_2OH)(1,2)$ , an alcohol obtained from the hydrolysis of salicin, a glucoside found in willow bark (for synthesis from phenol, see page 501).



Coumarin is made from it by the Perkin reaction. The reaction of salicylic aldehyde with acetic anhydride and sodium acetate gives *o*-hydroxy-cinnamic acid, which passes to its lactone, coumarin (see page 532).

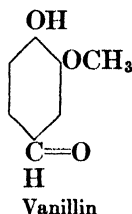
**Anisaldehyde** is made by the oxidation of anethole



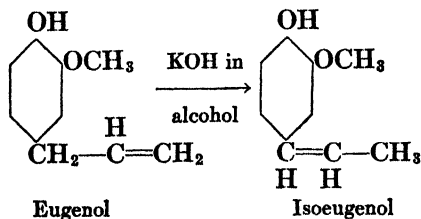
Etc.

with potassium dichromate and sulfuric acid. Anethole is a natural product found in oil of anise.

**Vanillin** is responsible for the pleasant odor of the vanilla bean. This substance may be made from guaiacol by the Reimer and Tiemann reaction. The compound eugenol, found in oil of cloves and other essential oils, may be changed to vanillin by the following series of reactions.



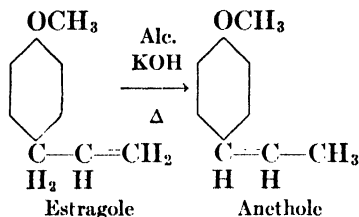
(a) When boiled with alcoholic potassium hydroxide, eugenol reverts to isoeugenol:



There are many examples of this type of reaction in which a double bond shifts to a position in which it will be conjugated with another double bond.



Another instance is that of estragole (methyl chavicol) obtained from tarragon oil, which shifts to anethole:



(b) Oxidation of isoeugenol (the OH group protected by acetylation) yields vanillin, in the same way that anethole gives anisaldehyde. Vanillin is also a hydrolysis product of lignin (page 379). The pulping of wood for paper manufacture gives large available stocks of lignin from which vanillin is now made commercially. Ethylvanillin,  $\text{C}_6\text{H}_3(\text{OC}_2\text{H}_5)(\text{OCH}_3)\text{CHO}$ , a synthetic product, is about three times as strong as vanillin and cheaper than vanillin.\*

In addition to its employment in the synthesis of vanillin, eugenol is used in dental preparations and medicines. It has a high antiseptic value.

The other aldehydes named above are used as synthetic agents and for the compounding of odorous mixtures.

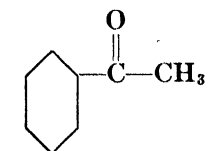
### KETONES

The aromatic ketones comprise three types of compounds, of which examples are given below. They are (1) aromatic-aliphatic ketones:

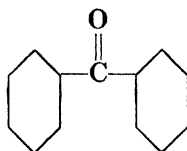
$\text{Ar}-\overset{\text{O}}{\parallel}{\text{C}}-\text{Alk}$ , (2) di-aromatic ketones whose groups are similar:  $\text{Ar}-\overset{\text{O}}{\parallel}{\text{C}}-\text{Ar}$ ,

and (3) di-aromatic ketones with unlike groups:  $\text{Ar}-\overset{\text{O}}{\parallel}{\text{C}}-\text{Ar}'$

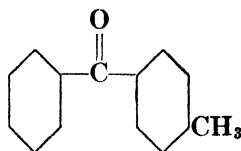
Examples:



Acetophenone, or  
Methyl phenyl ketone



Benzophenone,  
Diphenyl ketone

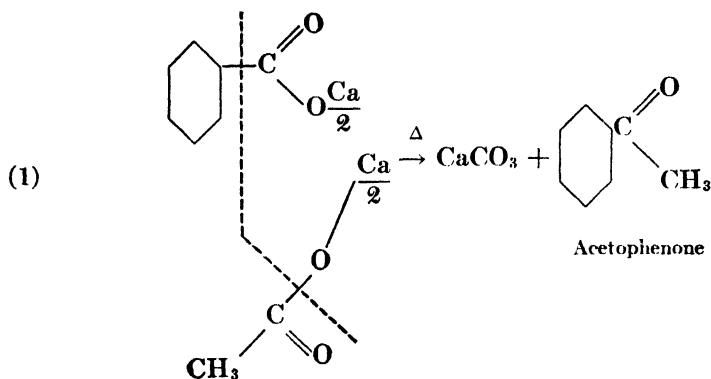


Phenyl-*p*-tolyl  
ketone

**Acetophenone.** Acetophenone is a typical representative of the mixed aliphatic-aromatic ketones. This compound is a colorless oil (m.p.,  $20.5^\circ$ ) with a fragrant aroma. The substance has been used as a hypnotic under the name "hypnone." It is also used in perfumes. A résumé of the

\* These facts now have especial meaning, for the Japanese (1942) have control of Java and Sumatra from which places comes oil of cloves.

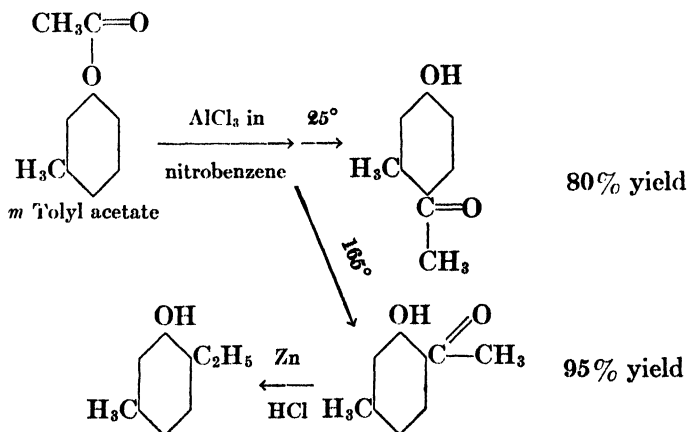
methods of preparation used for the aliphatic ketones shows the similarity of such a compound as acetophenone to acetone and other aliphatic ketones. Thus we may synthesize acetophenone by heating the calcium salts of benzoic and acetic acids:



(2) Preparation by oxidation of methylphenylcarbinol,  $\text{C}_6\text{H}_5\text{CHOH}\cdot\text{CH}_3$ .

(3) The best method of synthesis involves the reaction of acetyl chloride (or acetic anhydride) and benzene in the presence of dry aluminum chloride catalyst. This is an extension of the Friedel and Crafts reaction which is considered in detail in Chapter XXIX.

(4) **The Fries Reaction.** Aryl esters of carboxylic acids may be converted to hydroxyketones when treated under proper conditions with aluminum chloride. Important factors which govern the yield and the ring position to be substituted are the temperature and the nature of the solvent. It is possible that in the course of this reaction the ester is split and an acid chloride is formed which reacts with the aromatic ring as in the Friedel-Crafts reaction (page 578).

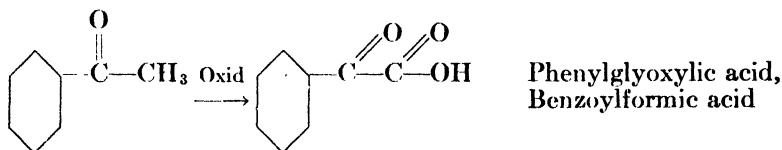


Reduction of the hydroxyketones gives alkyl phenols.

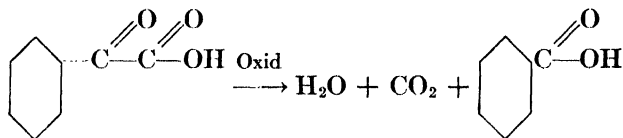
## REACTIONS

The reactions of acetophenone and related ketones are those to be expected of compounds similar in structure to acetone. They are presented below chiefly for the value of review.

(1) *Oxidation.* Mild oxidation, using cold permanganate solution, affects the alkyl group of acetophenone, which is oxidized to carboxyl group:



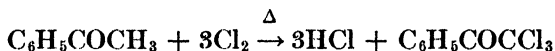
More thorough oxidation produces benzoic acid and carbonic acid ( $\text{CO}_2$  and  $\text{H}_2\text{O}$ ).



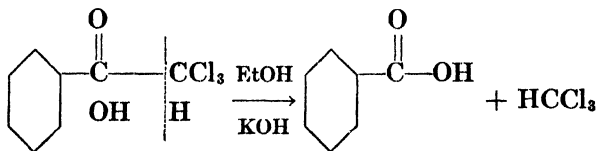
Acetone reacts in an analogous manner when oxidized with hydrogen peroxide.

(2) *The reduction of acetophenone yields methylphenylcarbinol.*

(3) *Halogens* react with acetophenone to replace hydrogen of the alkyl group:



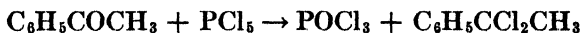
The hydrolysis of the chlorinated ketone produces benzoic acid and chloroform:



(Note reaction of acetone and iodine, page 157.)

$\omega$ -Chloroacetophenone,  $\text{C}_6\text{H}_5\text{COCH}_2\text{Cl}$ , phenacyl chloride, can be made from chloroacetyl chloride and benzene with aluminum chloride. It is a lacrymator, frequently used as a "mob gas."\*

(4) *By the action of phosphorus pentachloride*, the oxygen atom of acetophenone is replaced by two chlorine atoms:



\* For lists of compounds used as war gases, see pages 323 and 606.

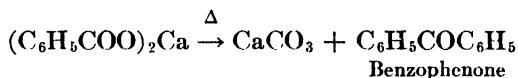
(5) *Acetophenone forms an oxime, phenylhydrazone, and a cyanohydrin* as could be predicted. It does not, however, unite with sodium bisulfite. This is possibly the result of steric hindrance by the phenyl group.

The hydrogen atoms of the methyl group are active and may be removed in condensations with other suitable compounds. Self-condensation yields dyponone,  $\text{C}_6\text{H}_5\text{C}(\text{CH}_3)=\text{CHCOC}_6\text{H}_5$  and symmetrical triphenylbenzene. These are analogous to mesityl oxide and mesitylene, formed from acetone (pages 155, 158).

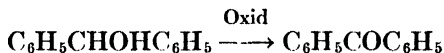
**Benzophenone.** We may use benzophenone, diphenyl ketone, as an example of a diaryl ketone. Benzophenone is a colorless solid whose odor is agreeable. It is used in perfumes.

Normally, a sample of the compound has a melting point of  $48.5^\circ$ , but it is sometimes secured with the melting point  $26.5^\circ$ . As there is but one possible structure for benzophenone we must liken this phenomenon to that observed in the case of elements like sulfur or phosphorus, which exhibit allotropy. As inferred above, the compound melting at  $48.5^\circ$  is the more stable, and is produced from the lower melting compound by inoculation with a trace of the  $48^\circ$  compound.

Benzophenone may be made by several methods similar in principle to those given for acetophenone. These are (1) Heating the calcium salt of benzoic acid:



(2) Oxidation of benzohydrol (diphenylmethanol):



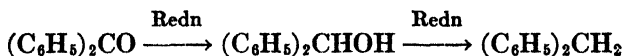
Diphenylmethane may be oxidized to benzophenone, just as triphenylmethane easily oxidizes to the carbinol (see page 492).

(3) The reaction of benzene with benzoyl chloride in the presence of aluminum chloride (page 578), is the best method for making benzophenone. Phosgene may also be used, or benzene and carbon tetrachloride may be treated to produce benzophenone dichloride,  $\text{C}_6\text{H}_5\text{CCl}_2\text{C}_6\text{H}_5$ , which is then hydrolyzed.

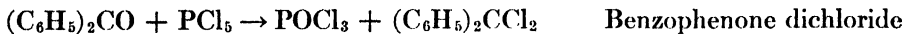
#### REACTIONS

(1) *Oxidation.* The oxidation of benzophenone destroys one of the benzene rings; benzoic acid is one of the products secured in this way.

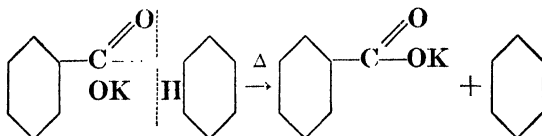
(2) *Reduction.* By partial reduction, benzohydrol is produced; complete reduction of benzophenone yields diphenylmethane:



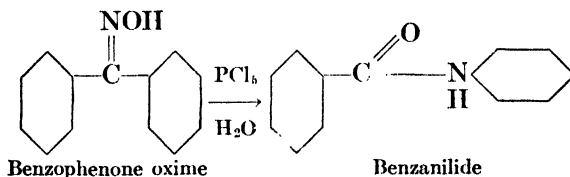
(3) *Phosphorus pentachloride* acts in the typical manner replacing oxygen by chlorine:



(4) *Fusion with potassium hydroxide* disrupts the molecule of benzophenone, resulting in the production of benzene and benzoic acid (salt).



(5) *Beckmann Rearrangement.* The oximes of benzophenone and other compounds of its class, when treated with  $\text{PCl}_5$  (followed by treatment with water), or with other acidic agents, undergo a remarkable shift or rearrangement, which transforms them to isomeric amides. The equation below shows this change as it takes place with benzophenone oxime:



Due to the influence of the reagents used, a shift occurs between the OH group and one of the aromatic groups.

This molecular shift, known as the Beckmann rearrangement, has been most intensively studied, but it is not yet thoroughly understood. The

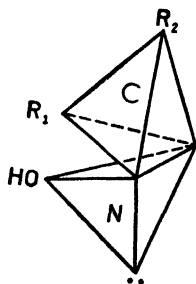


FIG. 85.

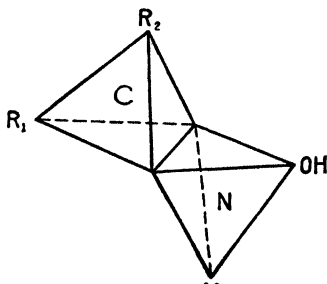


FIG. 86.

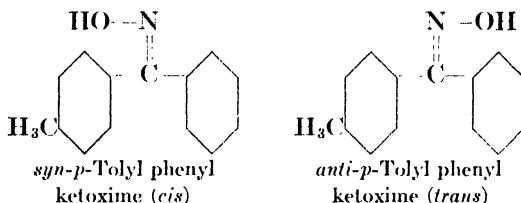
various theories in regard to the mechanism of the reaction will be found in the more advanced texts of organic chemistry.

In the case of many unsymmetrical ketones two oximes are known (two oximes are possible in all such cases, but often only one has been discovered).<sup>\*</sup> Where these substances exist, they are probably related to each

<sup>\*</sup> When the radicals attached to carbonyl are quite different from each other as in an aliphatic-aromatic oxime, only one form is produced.

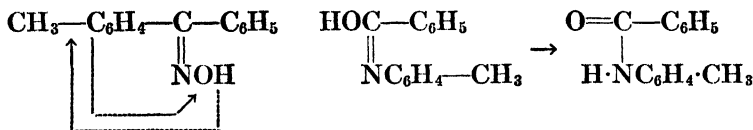
other as *cis-trans* isomers. We have the phenomenon of restricted rotation in cases in which carbon-carbon, carbon-nitrogen, or nitrogen-nitrogen are joined by a double bond. This was taken up on page 59 and more fully on page 328. The space formulas for two isomeric ketoximes according to this explanation are shown in Figs. 85 and 86.\*

The oximes of an unsymmetrical ketone like phenyl tolyl ketone would be shown in flat formulas as follows:

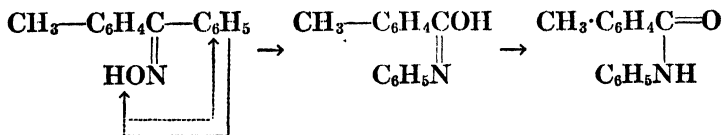


The nomenclature is that commonly employed. In the *anti* (*trans*) compound the key groups (tolyl and hydroxyl) are on opposite sides of the nitrogen atom, while in the *syn* (*cis*) compound they are on the same side.

It has been found that in the Beckmann transformation the shift occurs between the hydroxyl group of the oxime and the aromatic radical in the *trans* position. The reaction, therefore, enables us to determine the structure of the oximes of an unsymmetrical ketone. By inspection of the accompanying graphs it will be seen that the *anti* oxime, when subjected to the Beckmann reaction would yield the toluidide of benzoic acid:



while the *syn* oxime would in its turn yield the anilide of toluic acid:

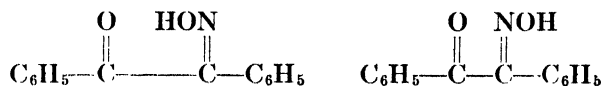


The nature of the substance secured in instances like the above is determined by the hydrolysis of the final products. In the first example cited, the hydrolysis would give toluidine and benzoic acid, whereas in the second case we would get aniline and toluic acid. These examples illustrate how the Beckmann transformation serves to distinguish between isomeric ketoximes.

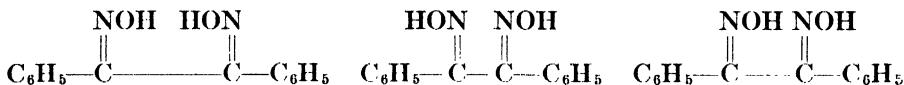
\* The models are somewhat distorted in order to accentuate the difference in structure between them.

The number of possible isomeric oximes increases with a diketone. Thus for benzil, the following are possible:

Two monoximes.



Three dioximes.



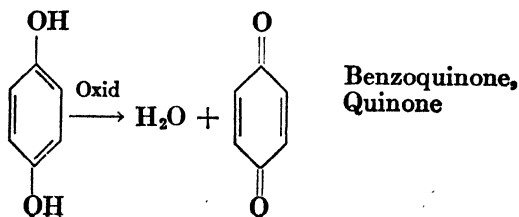
It is obvious that if one of the benzene rings were substituted, thus rendering the original compound unsymmetrical, the possible number of oximes would be larger.

### QUINONES

The discussion in this chapter to the present has shown that oxidation of primary and secondary alcohols whose carbon atom lies outside an aromatic ring, produces from them the aldehydes and ketones of the aromatic series. When the hydroxyl group is attached to a nuclear carbon, as in phenol, we have seen that oxidation gives different products according to the experimental conditions, often causing decomposition of the molecule.

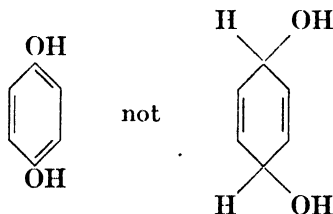
***p*-Benzoquinone.** With *p*-dihydroxybenzene, however, the case is otherwise. Its oxidation produces a derivative known as quinone, which evidently has two carbonyl groups, since it can form a dioxime. Moreover, the new compound may again be reduced to *p*-dihydroxybenzene, this standing as sufficient indication that the C=O groups produced in the oxidation are *para* to each other, also that the benzene ring has remained intact during the oxidation. The formula of quinone, C<sub>6</sub>H<sub>4</sub>O<sub>2</sub>, also testifies that the benzene ring has not been broken.

As the carbon atoms which form the C=O groups are also in the benzene ring itself, it is impossible that the new compound can have an arrangement of double and single bonds like that in benzene (benzenoid); this is precluded by the tetravalency of carbon. We are thus introduced to a new type of ring, called the quinone or quinonoid type, shown below:

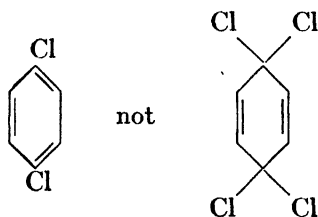


Quinone is a yellow crystalline compound, having a penetrating and irritating odor. It is slightly soluble in water, quite soluble in alcohol, ether, etc., and volatile in steam. As stated above, it may be made by oxidizing *p*-dihydroxybenzene. It also results when benzene *para* derivatives such as *p*-aminophenol, *p*-phenolsulfonic acid, *p*-phenylenediamine, etc., are oxidized. In the laboratory, quinone is sometimes made by the oxidation of aniline with potassium dichromate and sulfuric acid. The oxidation is quite complex. Polynuclear compounds related to dyes are formed, whose further oxidation is responsible for the production of quinone. A smoother synthesis results when hydroquinone is oxidized with potassium bromate. In the commercial production, benzene is electrolytically oxidized.

Quinone is included in this chapter because it has the  $\text{C}=\text{O}$  groups common to aldehydes and ketones. It forms both a monoxime and a dioxime, thus resembling a ketone. However, its reduction does not give the group  $=\text{CHOH}$  found in secondary alcohols, but produces instead hydroquinone, in which we have the group  $\equiv\text{COH}$  found in tertiary alcohols.



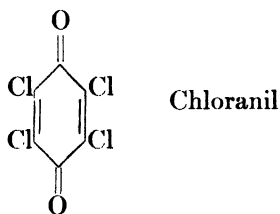
Moreover, when treated with phosphorus pentachloride, oxygen is not replaced by two chlorine atoms, but by one only:



In each case, the quinone ring reverts to the benzene structure.

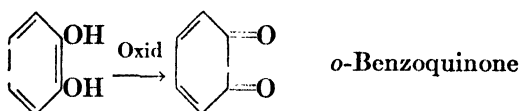
Quinone can add halogens or react by substitution, according to the experimental conditions. Chloranil, tetrachloroquinone, may be made by chlorination of quinone, or by action of potassium chlorate and hydrochloric acid upon aniline, phenol, *p*-phenylenediamine, and other compounds. It is an efficient oxidizing agent, used in the dye industry. Recent experiments have shown that chloranil is a seed protectant (fungicide) and growth stimulant for peas.





Quinone is, then, a derivative whose reactions are unique. As was the case with benzene, the reactions cannot be exactly predicted from the structure assigned to the compound. It does not behave entirely like a ketone, nor like an ethylene compound. The novel structure of quinone is supposed to account for its possession of color (yellow), especially as we note that many colored organic compounds and dyes possess rings of the quinone type.\*

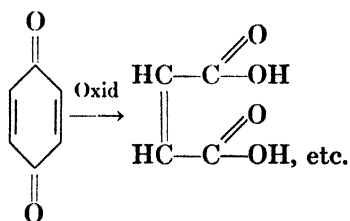
***o*-Benzoquinone.** The careful oxidation of *o*-dihydroxybenzene yields *o*-benzoquinone:



which is a red, odorless, crystalline, and non-volatile compound. *Meta* quinones cannot exist if they are to have structures like those of the *o*- and *p*-compounds.

**Review of Reactions.** The reactions of *p*-quinone may be summarized as follows:

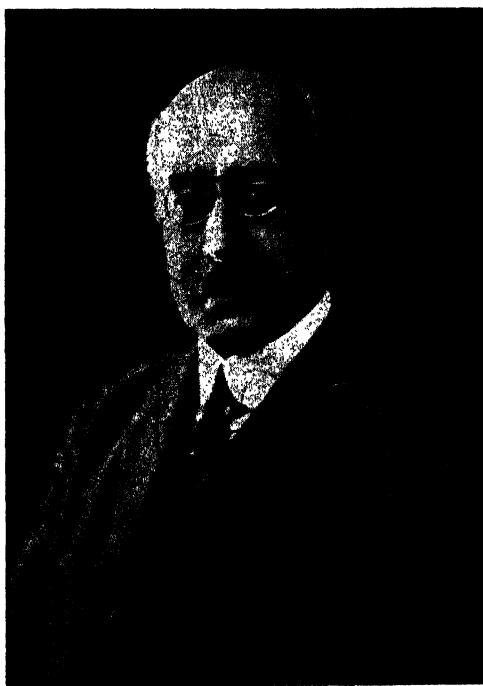
(1) *Oxidation* of quinone with silver peroxide yields maleic acid with other products. This may be considered as a confirmation of the structure which has been assigned to quinone.



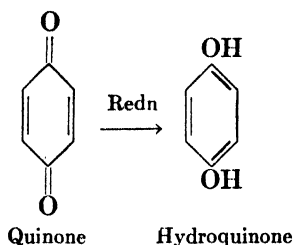
(2) *Reduction* is easily effected, with simultaneous change to the benzene type of nucleus:

\* For a definition of the term "quinone," see *J. Am. Chem. Soc.*, **62**, 757 (1940).

JULIUS STIEGLITZ. (1867-1937, American.) Stieglitz's early work was done with Hofmann, Tiemann, and Victor Meyer. He was interested in the mechanism of organic reactions and in the application of physical chemistry to organic chemistry. He worked with rearrangements, chromoisomerism, and electron theory. Stieglitz was for many years in charge of the department of chemistry of the University of Chicago. He was an excellent administrator. In addition he undertook editorial work (*Chemistry in Medicine*), for which he had undoubted gifts. He was one of the outstanding teachers of his time. See *J. Ind. Eng. Chem.*, **9**, 118 (1917), **24**, 587 (1932); *J. Am. Chem. Soc.*, **60**, 3 (1938).



MARSTON T. BOGERT. (American, 1868- .) Research on quinazolines, thiazoles, relation between odor and structure, and numerous other projects in all parts of the field of organic chemistry. Bogert has done an unusual amount of administrative work, heading many important national and international committees and commissions dealing with work of importance to American Chemistry. See *Ind. Eng. Chem.*, **25**, 591 (1933).

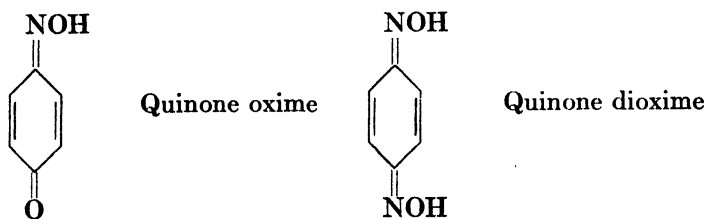


Because of its easy reduction, quinone is used as an oxidizing agent. Chloranil is also valuable in this way in situations which bar the use of inorganic oxidizing agents.

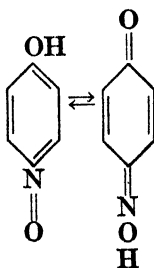
(3) *Halogens* give both addition and substitution compounds with quinone as already mentioned.

(4) *Phosphorus pentachloride* yields *p*-dichlorobenzene.

(5) *With hydroxylamine*, quinone forms quinone oxime, and quinone dioxime:



The monoxime is identical with *p*-nitrosophenol, which is also produced by the action of nitrous acid upon phenol. It passes by oxidation to *p*-nitrophenol. Quite evidently then, these compounds are tautomeric, the change from one to the other involving not only the migration of a hydrogen atom, but the alteration of ring type as well. The similarity with cases of keto-enol tautomerism already considered will be evident on inspection of the structures of the two compounds, quinone oxime and nitrosophenol:



The second of the above structures is considered more suitable for the compound, because quinone dioxime is formed from it, and because of its color, which accords better with quinone than with benzene structure.

There are many known instances of tautomeric shift in which a "benzenoid" ring becomes "quinonoid." Usually there is a deepening of color with the shift. This phenomenon is important in connection with the study of dyes.

(6) *Addition compounds.* Quinone forms addition compounds with a number of aromatic substances. The structure of most of these is uncertain.

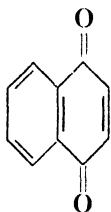
An example is phenoquinone formed from phenol and quinone. Quinhydrone is a green crystalline compound, formed by reaction of equal moles of quinone and hydroquinone. A practical use of the compound is for electrical determination of hydrogen ion concentration (quinhydrone electrode).

### QUINONES OF AROMATIC COMPOUNDS

In addition to benzene and its homologs, other aromatic compounds may yield derivatives of the quinone type, i.e., having C=O groups integral with their ring structures. The formulas of several of these are given on pages 597, 598.

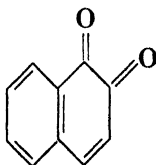
**Naphthalene.** Following are the three known quinone forms for naphthalene.

**$\alpha$ -Naphthoquinone, 1,4-Naphthoquinone.** This compound is formed by the oxidation of naphthalene. Like benzoquinone, it is colored yellow, sublimes readily, and is volatile in steam. Its odor is pronounced. Vitamin K (page 754) is a derivative of this quinone.



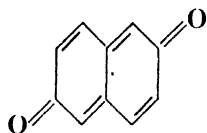
$\alpha$ -Naphthoquinone

**$\beta$ -Naphthoquinone, 1,2-Naphthoquinone.** Made by oxidation of the corresponding  $\beta$ -amino- $\alpha$ -hydroxynaphthalene. This substance resembles  $\alpha$ -benzoquinone in being odorless and non-volatile. Its color is red.



$\beta$ -Naphthoquinone

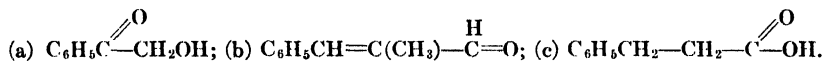
***amphi*-Naphthoquinone, 2,6-Naphthoquinone.** Prepared by oxidation of the corresponding dihydroxynaphthalene. This is a red, odorless, non-volatile compound.

*amphi*-Naphthoquinone

Other quinone-type compounds are anthraquinone, acenaphthenequinone, and phenanthrenequinone, which will be discussed later.

### REVIEW QUESTIONS

1. Write graphic formulas for the following: (a) Benzohydrol; (b) *o*-Tolualdehyde; (c) *o*-Chlorobenzophenone; (d) *p*-Tolyl phenyl ketone; (e) Hydrobenzoin.
2. Write equations for the formation of benzaldehyde (three methods) and for its reactions with: (a) Hydroxylamine; (b)  $\text{NH}_3$ .
3. Show structures of the derivatives secured by the reaction of benzaldehyde with: (a) KCN solution; (b) A reducing agent; (c)  $\text{H}_2\text{SO}_4$ ; (d) Phenol; (e) Propionaldehyde (see page 149).
4. Write equations for the formation of the following derivatives from benzaldehyde: (a) Benzoic acid (two methods); (b) Desoxybenzoin; (c) Dibenzalacetone; (d) Cinnamic acid.
5. Illustrate by the use of equations two methods of preparing an aromatic ketone.
- (R)6. Write sequences of equations for the preparation of the following compounds. (a) Phenyl benzyl ketone; (b) *p*-Chlorobenzophenone; (c) Ethyl-*p*-chlorophenyl ketone.
7. Give equations for two reactions of acetophenone which are common to acetone.
8. Write equations for the action of the following reagents upon acetophenone: (a) HCN; (b)  $\text{NH}_2\text{OH}$ ; (c)  $\text{C}_6\text{H}_5\text{NHNH}_2$ .
9. Show two methods by which benzoic acid may be produced from benzophenone.
10. Show structures of the oximes of phenyl *p*-chlorophenyl ketone and explain how they could be identified through the use of the Beckmann transformation.
11. Discuss the isomerism of the benzaldoximes.
12. How many oximes could theoretically be formed by benzoin?
13. Cite two reactions of quinone which support the ethylene structure for this compound, and one which is unusual for such a structure.
14. Show by equations the methods by which the following compounds may be prepared:



15. Set down in the form of a table those properties and reactions which distinguish from each other: quinone, benzaldehyde, acetophenone.
16. How would you proceed to separate a mixture of benzophenone and toluic acid? Of acetophenone and toluene?
17. How make: (a) Benzene from *o*-ethyl-benzaldehyde? (b) Benzamide from benzaldehyde? (c) Benzanilide from acetophenone?
18. How should the following compounds be converted to benzaldehyde: toluene; benzoic acid; benzyl alcohol?
19. Show by the use of equations how to convert benzaldehyde to toluene; to benzoyl chloride.
20. In view of the results with anethole and isoeugenol, what should be formed by mild oxidation of cinnamic acid?
21. Which of the hydrocarbons listed on page 408 might give benzaldehyde on gentle oxidation?
22. A certain substance which is not oxidized by air undergoes such oxidation when mixed with benzaldehyde. Offer an explanation for this.

23. Show by a diagram the formation of triphenylbenzene by the self-condensation of acetophenone.
24. Which of the methods presented for making benzophenone is, in your opinion, the least desirable? Why?
25. Show by the use of equations the various rearrangements listed in this chapter.
26. Dimethylquinone may be formed by the self-condensation of biacetyl. Show how this proves the structure of the quinone ring.
27. Show how to make 1-methyl-2-propylbenzene from phenol.
28. Write equations showing how to make: (a) Propyl phenyl ketone (by heating of the proper salts); (b) *p,p'*-Diethyl benzophenone from ethylbenzene, etc.
29. A compound of formula  $C_8H_7OCl$  reacts with HCN and with  $NH_2OH$ . It is capable of reduction. Its oxidation yields *p*-chlorobenzoic acid. Use these facts to establish a probable structure for the compound.
30. Show by equations the synthesis of coumarin from toluene and any necessary inorganic and aliphatic organic compounds.
31. List the reactions given in this chapter which are named for chemists.
32. Make a table of compounds listed in this chapter, putting in separate lists the compounds used for perfumes, for oxidizing agents, for identification of aldehydes and ketones, for other purposes.
33. What physical and chemical properties are of use in characterizing an aromatic aldehyde such as benzaldehyde? What derivative should be used in the identification?
34. Apply question 33 to a ketone of the type of acetophenone.
35. Write equations for the following preparations.
  - (a) *m*-Nitrobenzaldehyde from benzene;
  - (b) Hydrobenzamide from toluene;
  - (c) Acetanilide from benzaldehyde;
  - (d) Phenacyl chloride from benzene;
  - (e)  $C_6H_5C(OH)(CN)C_2H_5$  from benzene.
36. What compounds should be formed by interaction of the following substances?
  - (a) Anisaldehyde, acetic anhydride, and sodium acetate;
  - (b) Benzoin and excess phenylhydrazine;
  - (c) Salicylic aldehyde and acetaldehyde;
  - (d) *o*-Cresol, chloroform, and NaOH solution;
  - (e) *p*-Toluic aldehyde and cold concentrated KOH solution.
37. An organic compound of formula  $C_{14}H_{13}NO_2$  was treated with  $PCl_5$  and subsequently with NaOH solution, etc. It was possible in this way to isolate aniline and *p*-methoxybenzoic acid. What was the original compound?
38. How could the following mixtures be separated into the pure components?
  - (a) Benzaldehyde, butyl ether, chlorobenzene;
  - (b) *o*-Tolualdehyde, benzoic acid, *n*-octane;
  - (c) Nitrobenzene, benzaldehyde, carbon disulfide;
  - (d) Acetophenone, dimethylaniline, benzoic acid.
39. The organic compound (A) which contains 71.39% C, 5.03% H, 7.32% O, and 16.24% Cl, may be oxidized to the compound (B) which has the same formula as (A) minus two hydrogen atoms. Reaction of (B) with hydroxylamine gives a solid which is submitted to the Beckmann reaction, followed by hydrolysis. Aniline and *p*-chlorobenzoic acid are isolated in this experiment. Explain how these facts help to clear up the structure of (A).
40. Some of the bottles on the B-shelf of the organic stockroom have lost their labels. It is known that the bottles contain the following pure substances: benzaldehyde, benzamide, benzene, benzenesulfonyl chloride, benzoic acid, benzonitrile, benzoyl chloride. Describe briefly but in sufficient detail how each of these might be identified for relabeling.

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## CHAPTER XXIX

# GRIGNARD AND FRIEDEL-CRAFTS REACTIONS

## GRIGNARD REACTION

In 1899 Barbier first noted that in the reaction between methylhepten-

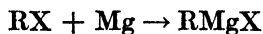
one,  $(\text{CH}_3)_2\text{C}=\overset{\text{H}}{\text{C}}-(\text{CH}_2)_2-\overset{\text{O}}{\underset{\text{||}}{\text{C}}}-\text{CH}_3$ , methyl iodide, and magnesium, in ether solution, a compound of formula  $\text{CH}_3\text{MgI}$  seemed to have been created, which then reacted with the ketone. The final product was the

tertiary alcohol, dimethylheptenol,  $(\text{CH}_3)_2\text{C}=\overset{\text{H}}{\text{C}}(\text{CH}_2)_2-\overset{\text{OH}}{\underset{|}{\text{C}}}(\text{CH}_3)_2$ . Alkyl

magnesium compounds like dimethylmagnesium,  $\text{Mg}(\text{CH}_3)_2$ , and diethylmagnesium,  $\text{Mg}(\text{C}_2\text{H}_5)_2$ , had been known before this time, but their preparation and use in synthetic work was a troublesome procedure.

Victor Grignard in 1900 began the investigation of the possibilities of compounds of the type  $\text{RMgX}$  in synthetic work, which has since that time enlisted the interest of scores of researchers, because of the constantly enlarging sphere of usefulness of these compounds.

**Preparation.** In preparing the Grignard reagent an alkyl or aryl halide, dissolved in perfectly dry ether, is added to the calculated amount of clean magnesium turnings, which are covered with pure dry ether and contained in a flask under an efficient reflux condenser. Iodides and bromides are apt to enter into reaction more readily than the chlorides, while certain aryl halides do not react spontaneously. A few crystals of iodine, or a small amount of methyl iodide, often suffices to start the reaction when it does not set in of itself.



The reaction is exothermic, and once started it frequently tends to go out of bounds, and requires cooling to prevent a too violent boiling of the ether. The magnesium compounds are soluble in ether, and the further use of these reagents does not require their isolation; the ether solution is used directly, after separation from the few scraps of magnesium which may be left.

The Grignard reagent can form in the absence of a solvent. It can also form in an inert solvent such as benzene. However the reaction proceeds more smoothly in an ether. Ethyl ether is probably used most often, though higher ethers are suitable, including anisole.



It is supposed that the Grignard reagent and the ether combine. Thus, the addition of a Grignard compound to ether liberates heat; also when an ether solution of Grignard reagent is evaporated a solid "etherate" is obtained, from which the ether can be removed only with great difficulty, as by heating to 100° or a higher temperature. However, in spite of the effort expended in research, the nature of this combination is still unknown.

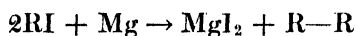
The Grignard compound apparently exists in solution in equilibrium with magnesium dihalide and dialkyl (diaryl) magnesium compound:



It is possible that other equilibria also are present; it is, however, satisfactory for our purpose to give the Grignard compound the formula  $\text{RMgX}$ .

A possible loss in yield during a Grignard reaction is due to the tendency of the Grignard complex to act as a reducing agent. For example, a 56% yield of benzyl alcohol can be obtained from reaction of benzaldehyde and isobutylmagnesium bromide; ethylmagnesium bromide gives 60%.\*

The formation of the Grignard reagent with alkyl halides is hindered by a side-reaction similar to the Wurtz reaction:



Even slight traces of moisture encourage this reaction, hence all reagents must be most carefully dried. Air (oxygen) must also be excluded. The tendency to undergo the Wurtz reaction is least for the alkyl chlorides and greatest for the iodides, and it increases with length of alkyl chain and with branching of the chain.

The second step of a Grignard reaction consists of the mixing of the ether solution of the prepared reagent with the desired aldehyde, ketone, or other substance. Dilution of the latter with ether before the mixing is often desirable. The reaction at this point is sometimes strongly exothermic. When it is complete, the resultant mixture is treated with cracked ice until decomposition is effected. The precipitation of magnesium salt is avoided by the addition of hydrochloric or other acid. Finally the desired reaction-product is removed and purified by distillation or otherwise, according to its properties.

Carbon dioxide, oxygen, and moisture must be excluded during the Grignard reaction up to the hydrolysis phase. It will be inferred from the description above that the Grignard reaction is not well adapted to large-scale industrial work. This situation arises partly from the technical difficulties involved, partly from the cost of the magnesium. A few industrial applications are known.

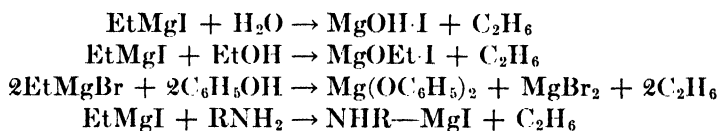
Grignard reagents are decomposed by substances containing OH and  $\text{NH}_2$  groups, and they add to the  $\text{C=O}$  group and other similar unsatu-

\* This action may be due to the Grignard reagent or to another compound formed in the course of the reaction.

rated unions. They also react with inorganic salts of mercury, antimony, lead, and other metals. In the following review of these reactions the Grignard reagents are shown as simple compounds, not as oxonium salts. This is common practice, since it makes for simplicity; it is justified by the fact that the ether is not actively consumed in the ensuing reactions.

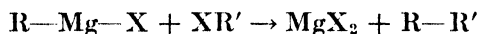
#### SYNTHESES WITH THE GRIGNARD REAGENT

(1) **Formation of Hydrocarbons.** The Grignard reagent is decomposed by water, alcohols, phenols, or amines, thioalcohols, acetylenic compounds; in each case liberating the hydrocarbon corresponding to its alkyl or aryl group.

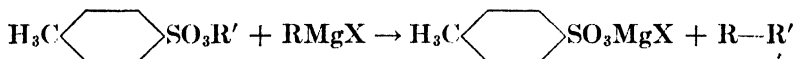


The Grignard reagent is used to detect amino, hydroxyl, or thiol groups in a compound, and may also be employed to estimate their number. The compound is heated with methylmagnesium iodide in a suitable solvent, and the evolved methane is measured (Zerewitinoff method).

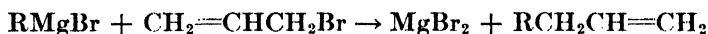
As has been stated the Grignard reagent can form a hydrocarbon by following the order of the Wurtz reaction. It differs from the Wurtz reaction in that different or similar radicals may be united with equal simplicity; in the Wurtz reaction the use of different radicals reduces the yield through the formation of by-products (page 81).



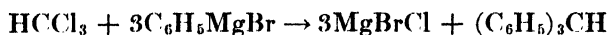
A modification of the reaction, using esters of toluenesulfonic acid gives better yields:



An ethylenic compound (a 1-alkene) may be formed by reaction with an allyl halide:



Triphenylmethane may be synthesized from phenylmagnesium bromide and chloroform:



Tetraphenylmethane is made as follows but in very small yield:



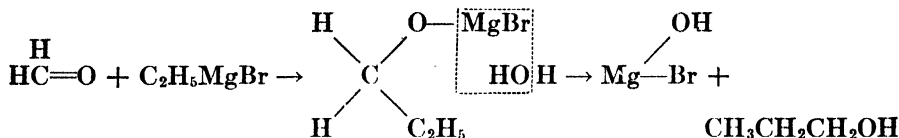
Methyl sulfate may be used to introduce the methyl group into a hydrocarbon through the Grignard reaction:



(2) Addition Reactions of the Grignard Reagent, Etc.

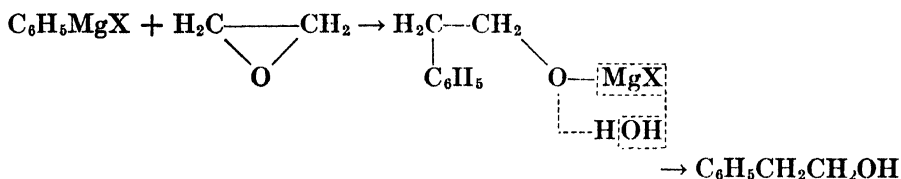
(a) Additions to the  $\text{C}=\text{O}$  group.

*Primary alcohols* are formed from the action of formaldehyde (or better, trioxymethylene) and Grignard reagents:



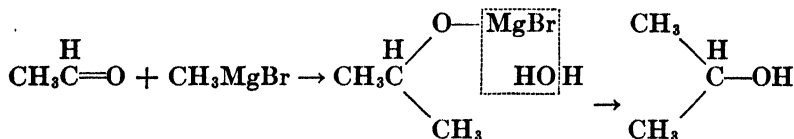
Note that there is a certain analogy between this reaction and the reaction between an aldehyde (ketone) and  $\text{HCN}$ ,  $\text{HNH}_2$ , etc. The more positive part of the Grignard reagent attaches to the oxygen atom, and the more negative part to carbon.

A primary alcohol with *two additional carbons* is formed by the use of ethylene oxide:



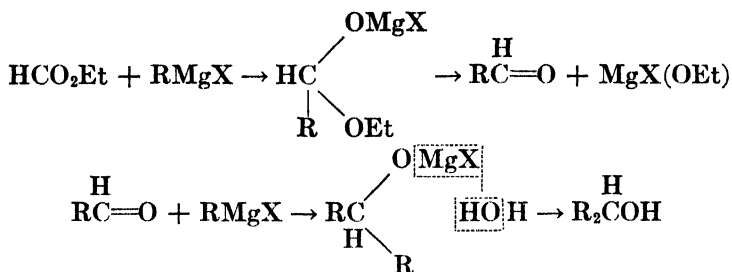
The by-product in the final hydrolysis of Grignard intermediate compounds is always  $\text{Mg}-\text{OH}$ . For this reason only the organic compound formed in each case is shown as a product of the reaction in the equations which follow.

*Secondary alcohols.* These are formed from the Grignard reagent and an aldehyde other than formaldehyde:

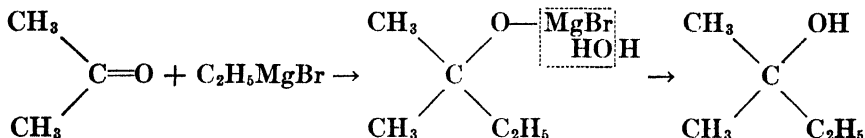


When Grignard reagents combine with esters of formic acid, secondary alcohols are formed:

\* In the presence of a mineral acid the  $\text{OH}$  ion is suppressed, and the solution contains a magnesium salt of the acid concerned.

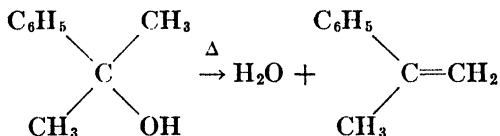


*Tertiary alcohols* result from the action of ketones with the Grignard reagent:



This reaction frequently produces an unsaturated hydrocarbon, due to loss of water by the tertiary alcohol.

Example:



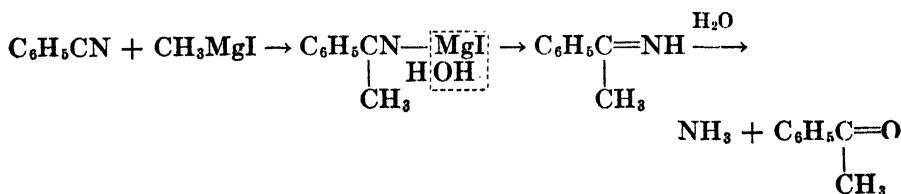
When this outcome is desired it can usually be brought about by simple means; or, by varying the experimental conditions, it may be avoided in many cases.

Reaction of Grignard compounds with esters (not formates) or organic acids, also gives tertiary alcohols.

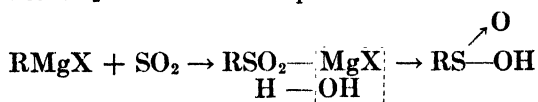
Acid chlorides give both *ketones* and *tertiary alcohols*, the relative proportions being determined by the nature and concentration of the reactants.

(b) Addition to CN group.

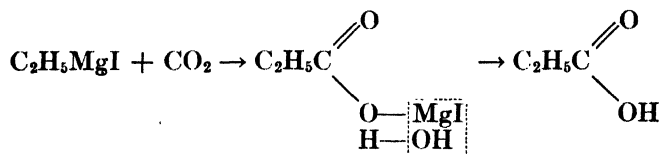
*Ketones* are made from the reaction between nitriles and the Grignard reagent:



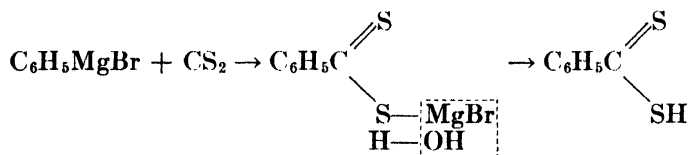
(c) Addition to  $\text{SO}_2$ . The reaction produces a sulfinic acid:



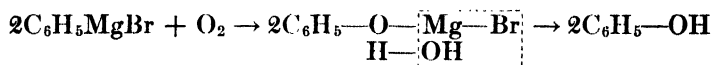
(d) Other addition reactions, etc. Carbon dioxide and carbon disulfide react alike toward the Grignard reagent. The former produces a *carboxylic acid*:



From carbon disulfide we obtain the *carbodithioic acids*:

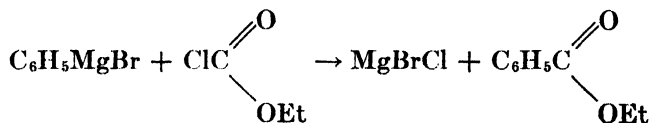


With oxygen, *alcohols* and *phenols* are formed:



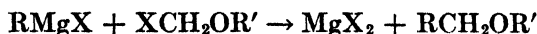
Alkylmagnesium halides give alcohols in good yield upon oxidation, but the arylmagnesium halides give small yields of phenols. Sulfur reacts analogously; the yield of *thiophenol* is good.

(e) It is possible in certain cases to form *esters* from the Grignard reagent, by employing the esters of chloroformic acid:

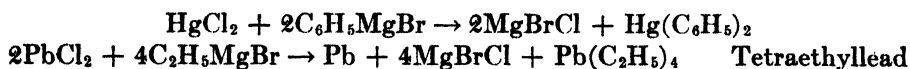


Other methods are also used.

(f) *Ethers* are formed as follows:



(3) **Organometallic Compounds.** Alkyl and aryl derivatives of many metals may be obtained by use of the Grignard reagent as illustrated herewith:



Further examples of such reactions will be found in the section on organo-metallic compounds, page 325.

The above equations show some of the many applications to synthetic work of the Grignard reaction, and sufficiently indicate its versatility. For further possibilities of this important reagent, the student is referred to the technical journals and larger texts.

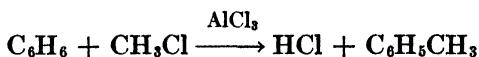
### THE FRIEDEL-CRAFTS REACTION

The basis of this important aid to organic synthesis is the reaction which takes place between an aromatic hydrocarbon and an aliphatic halogen compound, in the presence of dry aluminum chloride, by means of which hydrogen halide is split off, and a new derivative is formed. The reagents are brought together in carbon disulfide, petroleum ether, or some other anhydrous solvent. If an inexpensive liquid hydrocarbon is one of the reactants, an excess of this may be employed for solvent purposes. In industrial applications the reaction is often carried out in a mill in which the solid reactants are ground and intimately mixed, any liquid reactant being added from time to time. This method allows close control of the temperature and is economical since very little or no solvent is employed.

At the close of a Friedel-Crafts reaction the complex aluminum compounds are hydrolyzed with cold water and acid, and the product is isolated by a suitable method (distillation, etc.). If a very small amount of aluminum chloride has been used in the reaction the hydrolysis may be omitted; in some cases of this kind the catalyst may be separated and reused.

Hydrocarbons and derivatives of the benzene, naphthalene, and other aromatic series participate in this reaction with alkyl halides, and with the acid chlorides of both the aliphatic and aromatic series. Several important classes of substances result from the reaction.\* These are:

(1) *Homologs of benzene.* Toluene is formed when aluminum chloride acts upon a mixture of benzene and methyl chloride:

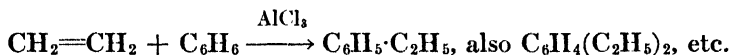


By continued action xylene is formed, and even three or more side-chains may be introduced. Such a mixture is separated into its components by fractional distillation. It must also be noted that this reaction is reversible; xylene, boiled with aluminum chloride in benzene solution, reverts in part to toluene, the latter again producing benzene and xylene. Hexamethyl-

\* This description refers to the original conception of the Friedel-Crafts reaction. The scope of the reaction has been so much increased that it would now be better to speak of Friedel-Crafts "Syntheses." The method has now been applied to aliphatic compounds, and with an increasing number of successful syntheses in this field the original "aromatic" conception will probably be lost. For examples of aliphatic reactions, see References 19 and 20. An example of a reaction not covered by the original conception of the Friedel-Crafts reaction is that between an aromatic acid and an aromatic hydrocarbon.

benzene, if mixed with aluminum chloride and heated in a current of hydrogen chloride, loses its methyl groups in succession, forming finally, benzene.

Olefins may also be condensed with rings to give benzene homologs:

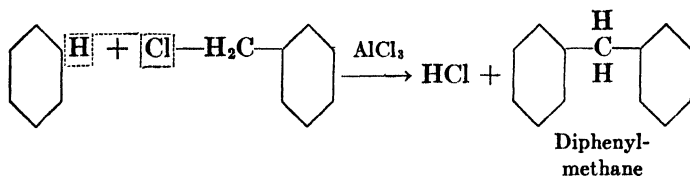


Other effective catalysts for this synthesis are boron fluoride or 90–100% sulfuric acid.

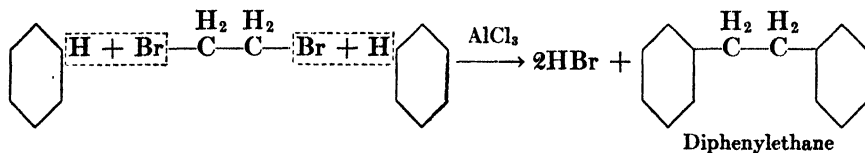
Aryl halides will not react with aliphatic hydrocarbons, i.e., phenyl chloride will not react with methane to yield toluene; however compounds like benzyl chloride, in which the halogen atom forms part of a side-chain, and which as we have stated are essentially aliphatic in nature, do take part in the Friedel-Crafts reaction.

Aromatic nitro compounds do not take part in the Friedel-Crafts reaction, nor do benzoates. Certain other compounds with “negative” groups will not react.\* If the Friedel-Crafts reaction is carried out with a substituted ring the orientation of the entering group is usually “normal.” But there are exceptions and this cannot be taken for granted. Alkyl halides with long chains usually rearrange during the reaction to give a branched-chain halide. This restricts alkylations to the use of short chain (methyl and ethyl) halides. Variables affecting the course of a Friedel-Crafts reaction are the temperature, the solvent, the catalyst, and the reactants.

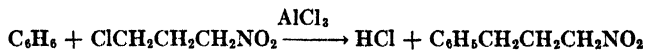
(2) *Other hydrocarbons.* The use of benzyl chloride with benzene leads to the production of diphenylmethane:



Diphenylethane is produced by the reaction between ethylene dibromide and benzene:

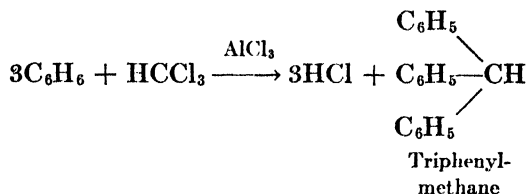


\* It has recently been shown that chloronitroparaffins may be used in a Friedel-Crafts reaction with benzene. An example is:



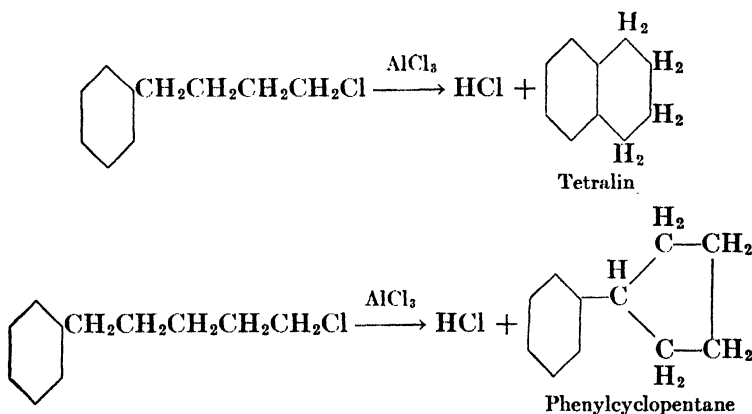
This application of the Friedel-Crafts reaction has very interesting possibilities.

With benzene and chloroform we get triphenylmethane:

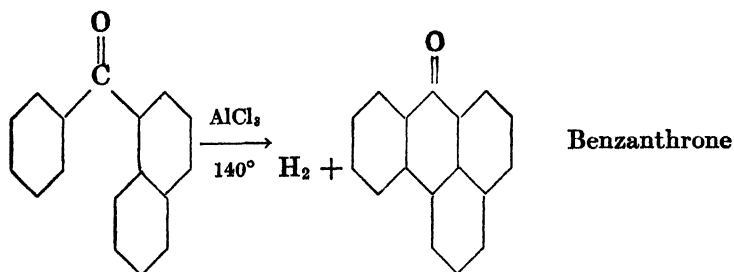


Carbon tetrachloride does not yield tetraphenylmethane when brought into reaction with benzene. The compound may, however, be made by other means (page 571).

If the side-chain on a ring has the proper length to yield a stable ring (page 610), ring closure may occur:

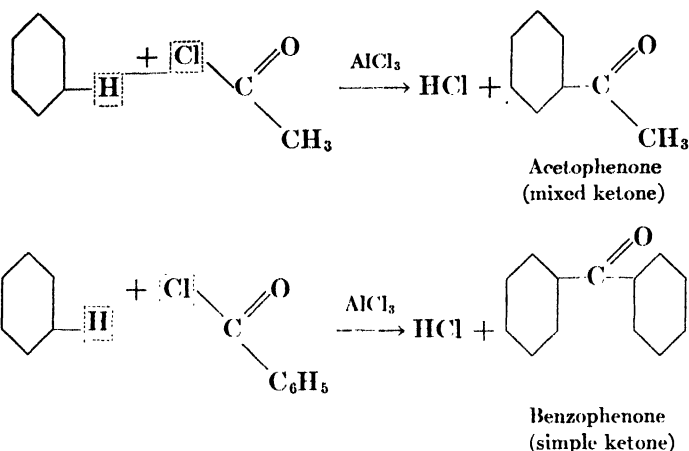


Aluminum chloride is a valuable reagent for inducing the condensation of aromatic rings (Scholl reaction). An example is seen in the conversion of phenyl  $\alpha$ -naphthyl ketone to benzanthrone:

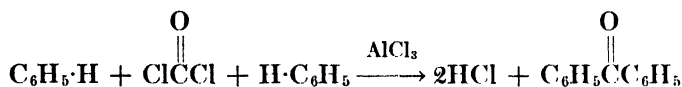


(3) *Ketones*. (a) Ketones are formed by the action of acid halides (aliphatic or aromatic) upon aromatic hydrocarbons. An example of each type is given:

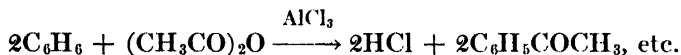




(b) The use of phosgene may lead to the formation of an acid chloride (see p. 522), or a simple ketone:



(c) Acid anhydrides also give ketones:

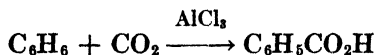


In this reaction the aluminum chloride appears to act as a chlorinating agent, converting the acid anhydride to acid chloride, which then reacts in the normal way. (d) A carboxylic acid treated with a ring compound in presence of aluminum chloride gives a ketone, probably after a preliminary transformation to the acid chloride.

(4) *Aldehydes.* An aldehyde may be synthesized from an aromatic hydrocarbon by mixing it with aluminum chloride and cuprous chloride, and bringing it into reaction with a mixture of carbon monoxide and hydrogen chloride (see page 546).\*

(5) *Acids.* The reaction of an aromatic hydrocarbon with phosgene gives an acid chloride which may be hydrolyzed to yield an acid (p. 522).

Another synthesis of acids depends on the use of carbon dioxide:



The extremely important reaction of phthalic anhydride and benzene, giving *o*-benzoylbenzoic acid, is shown on page 594.

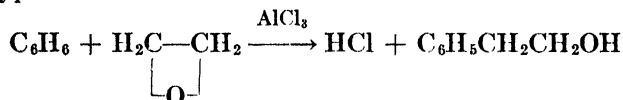
\* In a similar way a mixture of hydrogen chloride and hydrogen cyanide will react to give an aldehyde. The method is useful in placing the aldehyde group in phenols and aromatic ethers. This method and the CO-HCl method are due to Gattermann and Koch.

WILLIAM L. EVANS. (American, 1870-  
 .) Evans is emeritus professor of  
 chemistry in the Ohio State University;  
 he was head of the chemistry department  
 there for many years. He is author and  
 co-author of several chemistry textbooks.  
 His research interests lie in the carbo-  
 hydrate field and particularly in the  
 mechanism of carbohydrate oxidation.  
 See *Ind. Eng. Chem.*, (News Edition), **18**,  
 1118 (1940); *Chem. Rev.*, **31**, 537 (1942).



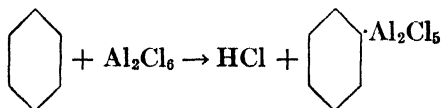
JAMES F. NORRIS. (1871-1940, Amer-  
 ican.) Norris was for many years in  
 charge of the research laboratory of  
 organic chemistry of the Massachusetts  
 Institute of Technology. He was an  
 outstanding teacher and also well known  
 through his textbooks of organic and  
 inorganic chemistry. He headed many  
 committees and boards charged with the  
 advancement of chemistry and the prose-  
 cution of the First World War. See *Ind.*  
*Eng. Chem.*, (News Edition), **14**, 325  
 (1936); **18**, 730 (1940)

(6) *Synthesis of Arylalkanols.* The preparation of  $\beta$ -phenylethyl alcohol is typical:

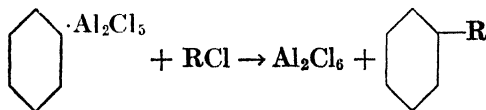


(7) *Other applications.* The following employments of aluminum chloride have been mentioned in previous pages: (a) cracking of petroleum (page 41); (b) isomerization of petroleum hydrocarbons (page 43); (c) alkylation of phenols (page 508); (d) formation of aromatic aldehydes (page 546); (e) Fries reaction (page 555). Other uses will be shown on later pages.

**Mechanism of the Reaction.** The examples cited show the more important uses of the Friedel-Crafts reaction and indicate its especial application to the aromatic series. Our knowledge of the true course of this reaction is still imperfect. It was thought by Friedel and Crafts that aluminum chloride united with the hydrocarbon:



and that this intermediate compound then interacted with the alkyl halide:

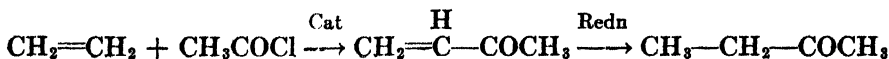


regenerating the aluminum chloride, which would thus be a true catalyst. If this conception is correct, a very little aluminum chloride should be capable of transforming large amounts of material.

In support of the theory we have the discovery of compounds of aluminum chloride and hydrocarbons, such as  $\text{Al}_2\text{Cl}_6 \cdot 6(\text{C}_6\text{H}_6)$ .

Another theory assumed that aluminum chloride functions as a true catalyst, but also unites with the reaction-product to some extent, and for this reason more of the substance must be used than if it acted only as a catalyst. In practical work the ratio of aluminum chloride to reactant varies from a few per cent to several hundred per cent, according to the type of reactant, and no one theory would suffice to explain this variation.

**Applications of Friedel-Crafts Reaction to Aliphatic Compounds.** The Friedel-Crafts reaction has been applied to the reaction of acid chlorides with saturated aliphatic hydrocarbons and with cycloparaffins. Yields were not good. Condensations of olefins with acid chlorides yield ketones:



For other aliphatic applications see references 13 and 20. The scope of the Friedel-Crafts syntheses has increased tremendously in the sixty-five years during which the method has been used. Many catalysts are used in place of the original aluminum chloride (chlorides of Fe, Zn, Sn, B, etc.), and condensations far different from those originally proposed are successfully accomplished. There is no present indication that the possibilities in this field have been exhausted.

### REVIEW QUESTIONS

1. Show by equations the synthesis of the following compounds through the Grignard reaction: (a)  $\text{C}_2\text{H}_5\text{COOH}$ ; (b) Hexane from hexyl bromide; (c) Diphenylethane; (d)  $(\text{C}_6\text{H}_5)_3\text{C}-\text{CH}_2\text{C}_6\text{H}_5$ .
2. Write equations showing the synthesis of the following compounds by means of the Grignard reaction: (a)  $\text{C}_6\text{H}_5\text{CSSH}$ ; (b)  $\text{C}_2\text{H}_5\text{CH}_2\text{OH}$ ; (c)  $(\text{C}_2\text{H}_5)_3\text{C}-\text{OH}$ ; (d)  $\text{CH}_3-\text{CHOH}-\text{C}_2\text{H}_5$ ; (e)  $\text{C}_6\text{H}_5\text{COOC}_2\text{H}_5$ ; (f)  $\text{C}_6\text{H}_5\text{C}(\text{C}_2\text{H}_5)=\text{CH}_2$ ; (g) Phenol; (h)  $\text{C}_6\text{H}_5\text{COOMe}$ .
3. Show how the Friedel-Crafts reaction may be used to make: (a)  $\text{C}_6\text{H}_5\text{C}_2\text{H}_5$ ; (b) Diphenylethane; (c)  $\text{C}_6\text{H}_5\text{COC}_2\text{H}_5$ ; (d) Benzoic acid.
4. Illustrate the use of the Friedel-Crafts reaction in the preparation of: (a) *p*-Bromoacetophenone; (b) *p*-Methoxyacetophenone.
5. Indicate how the Grignard reaction may be employed to make: (a) A phenol; (b) Ethane; (c) A carbodithioic acid.
6. State the theories bearing on the function of aluminum chloride in the Friedel-Crafts reaction.
7. What metals might replace Mg and Al in the two reactions discussed in this chapter?
8. Explain why moisture and carbon dioxide are barred in the preparation and use of the Grignard reagent.
9. Show the synthesis of *m*-nitrochlorobenzene from *m*-dinitrobenzene.
10. Show how to synthesize diphenylmethane from benzyl alcohol.
11. Show how to make benzylamine from  $\text{C}_6\text{H}_5\text{CH}_2\text{CH}_2\text{COC}_2\text{H}_5\text{COC}_2\text{H}_7$ .
12. Name all the compounds whose formation is shown in the section on Grignard reaction. In case a generalized formula is shown, supply formula and name of an actual compound to take its place.
13. Indicate by the use of equations how the following reagents would act upon ethylmagnesium bromide: (a)  $\text{H}_2\text{O}$ ; (b)  $\text{NH}_3$ ; (c) Acetone; (d)  $\text{MeOH}$ ; (e) Propionaldehyde; (f) Ethylene oxide; (g)  $\text{CS}_2$ ; (h) Oxygen.
14. What side-reactions may take place during the course of a Grignard reaction? What means may be used to avoid these side-reactions?
15. If we are to assume that a Grignard reagent ( $\text{RMgX}$ ) ionizes in solution, what ions may be present (according to the evidence given in this chapter)?
16. Write the formula for an oxonium salt formed from  $\text{EtMgI}$  and ethyl ether.
17. A 0.10 g. sample of a compound whose molecular formula is  $\text{C}_4\text{H}_{10}\text{O}_2$  gave 24.9 cc. of methane upon reaction with methylmagnesium iodide. How many OH groups are present in the compound?
18. A compound has the molecular formula  $\text{C}_8\text{H}_4\text{O}_6$ . A 0.130 g. sample when treated with methylmagnesium iodide gave 29.71 cc. of methane. How many active hydrogen atoms does the molecule possess?
19. In a certain synthesis phthalic anhydride was heated with aluminum chloride and toluene. The product was an acid (A) containing 75.0% C, 5.0% H, and 20.0% O. Upon proper treatment the compound (A) may be made to lose one molecule of water and undergo a condensation. Prove the structure of (A) and of its condensation product.

20. Write equations for the Grignard reactions in which the following compounds are used.
- n*-Butyl bromide and Mg; then ethylene oxide; then water, etc.;
  - 2-Chlorobutane and Mg; then CO<sub>2</sub>; then water, etc.;
  - Benzyl chloride and Mg; then diethyl sulfide; then H<sub>2</sub>O, etc.;
  - tert* Butyl chloride and Mg; then CO<sub>2</sub>; then H<sub>2</sub>O, etc.;
  - Bromobenzene and Mg; then antimony trichloride; then H<sub>2</sub>O, etc.
21. The organic compound (A) contains 30.51% C, 1.70% H, and 67.80% Br. Nitration yields but one mononitro compound. (A) was treated with metallic magnesium (ether); then with CO<sub>2</sub>; then with water, etc. In this way the compound (B) was produced. (B) contains 57.84% C, 3.62% H; the balance is oxygen. It is an acid with neutralization equivalent of 83. (B) has no definite melting point; it sublimes when heated above 300°C. It does not lose water when heated. What is the structure of (A)? What is a practical way to make (B)?

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## CHAPTER XXX

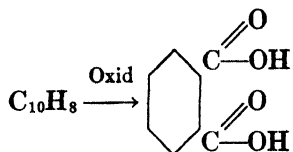
### NAPHTHALENE, ANTHRACENE, AND RELATED COMPOUNDS

During the processing of coal tar for benzene, toluene, and like compounds, from six to ten per cent of naphthalene is obtained. This compound fills an important place in synthetic work, being used to form phthalic anhydride, benzoic acid, and other derivatives which are used in the manufacture of dyes and in many other ways. Its yield from coal tar, larger than that of any other aromatic hydrocarbon, is commensurate with its importance.

Naphthalene,  $C_{10}H_8$ , is a white crystalline compound, having a peculiar penetrating odor. Although its boiling point is high ( $217.9^\circ$ ), it is volatile in steam, also it readily sublimes. Insoluble in water, it is easily soluble in hot alcohol, in ether, and other organic solvents. Aside from its synthetic uses the compound is used in "moth balls."\* Naphthalene has a limited medical use as an antiseptic and anthelmintic. Sales of naphthalene in this country in 1940 totalled 146,000,000 pounds.

#### STRUCTURE OF NAPHTHALENE

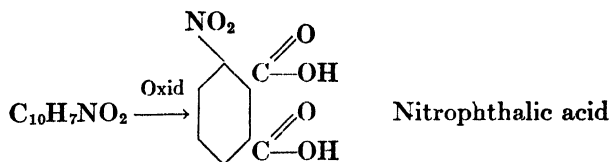
Naphthalene resembles benzene in its chemical properties. It reacts with halogens to form addition and substitution products. Nitric and sulfuric acids yield nitro compounds and sulfonic acids, as with benzene. The hydroxyl derivatives are similar in their properties to the phenols. Some knowledge of the structure of naphthalene is gained by a study of its oxidation, which is more easily accomplished than the oxidation of benzene:



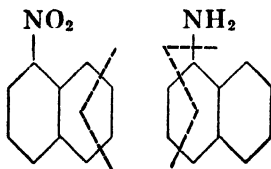
This results in the formation of *ortho* phthalic acid, no matter how the reaction may be promoted. Evidently the benzene ring is a part of the naphthalene molecule. If we subtract  $C_6H_4$  from  $C_{10}H_8$ , four carbons and four hydrogens remain; it seems very unlikely that these atoms form side-chains on a benzene ring. Such groups would be highly unsaturated to begin with; moreover, the reactions of naphthalene do not uphold such a structure.

\* *p*-Dichlorobenzene has largely displaced naphthalene in this role.

A study of nitronaphthalene and naphthylamine has shown how the remaining atoms are disposed. When mononitronaphthalene is oxidized nitrophthalic acid results:



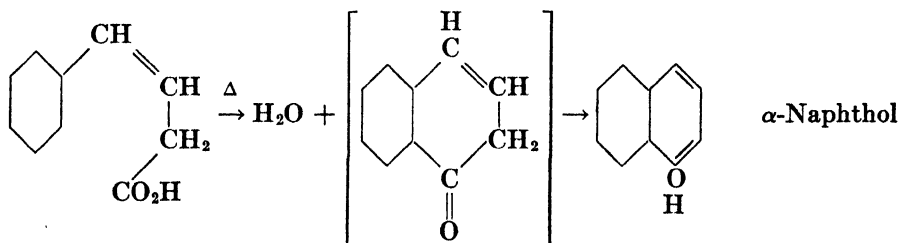
however if we reduce nitronaphthalene to naphthylamine and oxidize this compound, the benzene ring with its amino group is destroyed (it has already been emphasized that aromatic amines are more easily oxidized than nitro compounds or hydrocarbons). The product of this reaction is *ortho* phthalic acid. The only possible explanation of these results is that naphthalene contains *two benzene rings* which mutually share two adjoining carbon atoms. In the oxidation of nitronaphthalene the unsubstituted ring is oxidized:



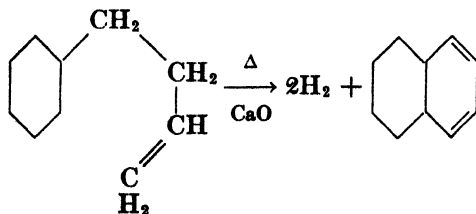
while the oxidation of naphthylamine leaves the unsubstituted ring intact. The dotted lines indicate the manner of oxidation in each case.

Additional proof for the structure assigned to naphthalene is found in the following syntheses:

(1) Naphthol from phenylisocrotonic acid (Fittig):



(2) Naphthalene from phenylbutylene or phenylbutylene bromide:





The disposition of the remaining valence bonds in the naphthalene formula is usually represented as shown here in Erlenmeyer's formula.

Three practically equivalent formulas can be written for naphthalene, and it is to be presumed that resonance occurs between the corresponding molecular forms. The resonance energy of naphthalene is 75 Kg. cal. per mole. As a consequence of resonance the bonds joining  $\alpha$  and  $\beta$  carbons have more "double-bond character" ( $\frac{2}{3}$ ) than those joining  $\beta$  and  $\beta$  carbons ( $\frac{1}{3}$ ). This may be read into the Erlenmeyer formula. The bonds of the benzene ring may be said to have about  $\frac{1}{2}$  double-bond character.

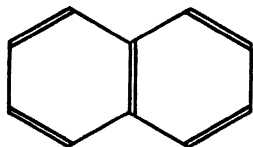


FIG. 87.—Erlenmeyer formula (1866).

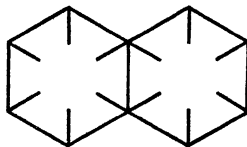


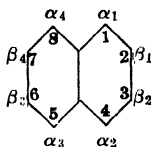
FIG. 88.—Bamberger formula.

The following statements are useful, though they admit of exceptions.

(1) Naphthalene is more easily reduced than benzene. (2) It adds halogen more readily. (3) All substitutions take place more readily until one ring is saturated or oxidized. (4) Groups are more easily removed from the ring than in benzene.

When one ring has become saturated or is broken by oxidation, the other becomes benzene-like, i.e., aromatic and stable.

**Nomenclature; Numbering of Rings.** Ordinarily the naphthalene formula is shown as two adjoining hexagons without indication of double bonds:



A structure such as this, in which carbon atoms are shared by two rings, is called a "condensed" structure. It will be noted that there are two structures for mono derivatives of naphthalene: positions 1 and 4, 5 and 8 are similar, also the four positions 2, 3, 6, and 7 are similar, but unlike the first four. Groups substituted in the first named positions give *alpha* compounds, while substitution in positions 2, 3, 6, or 7 gives a *beta* compound. When two like groups are introduced into the naphthalene molecule there are ten possibilities of isomerism; two unlike groups yield fourteen isomers, three like groups give fourteen isomers, four like groups give twenty-two isomers, etc.\* It is seen that the situation is more complex than with benzene.

\* For eight unlike groups the reported number of isomers possible is over 10,700,000. This includes all possible combinations of one to eight groups.

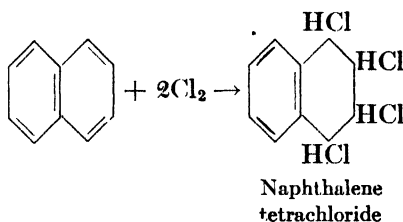
Groups in the same ring situated in adjacent positions are called *ortho*, while the 1-3 and 1-4 positions are termed *meta* and *para*, as with benzene. The 1-8 position is termed *peri*. Groups situated in this relation act like *ortho* groups in benzene (note anhydride formation of 1,8-naphthalic acid, page 538).

### REACTIONS OF NAPHTHALENE; DERIVATIVES

(1) *Alkyl derivatives*. Methyl-, dimethyl-, and trimethyl naphthalenes occur in coal tar. A related compound, naphthaleneacetic acid, is an important plant hormone.

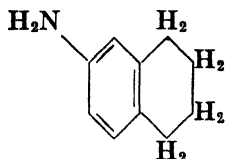
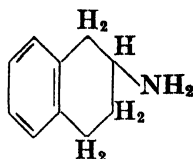
(2) *Halogen derivatives*. *Alpha* halogen derivatives of naphthalene are obtained by direct treatment at the boiling point of the hydrocarbon, or both *alpha* and *beta* derivatives may be had from the reactions of the corresponding naphthols with phosphorus pentachloride or pentabromide. Also the corresponding naphthylamines may be diazotized, and converted to halogen compounds by the Sandmeyer reaction.

When chlorine acts upon naphthalene at room temperature, addition takes place, and naphthalene tetrachloride is formed:



The addition is confined to one ring; this is proved by oxidation of the compound, which gives *ortho* phthalic acid as a product. Other derivatives similar to this are known, in which one ring has lost its double bonds while the other retains the benzene structure. When this is the case a substituent attached to the benzene ring yields a compound aromatic in character, while attachment to the reduced ring gives a compound with aliphatic character.

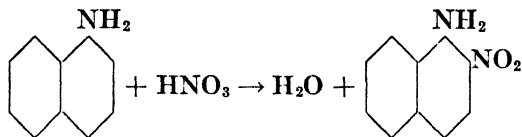
This is seen in the case of the tetrahydro- $\beta$ -naphthylamines. The compound with structure (1) below has the same character as aniline, while compound (2) is like an aliphatic amine. The names of the compounds show whether the  $\text{NH}_2$  group is joined to the aromatic (*ar*) ring or to the alicyclic (*ac*) ring. *Alpha* naphthylamine and *alpha* naphthol when reduced give the corresponding *ar*-tetrahydro derivatives, while the reduction of *beta* naphthylamine and *beta* naphthol gives principally *ac*-tetrahydro compounds.

(1) *ar*-Tetrahydro- $\beta$ -naphthylamine(2) *ac*-Tetrahydro- $\beta$ -naphthylamine

Continued chlorination of naphthalene leads to complex polymerization. A waxlike product known as Halowax is obtained. This has commercial uses.

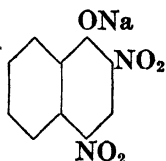
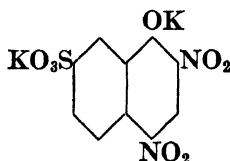
(3) *Sulfonic acids*. The naphthalene monosulfonic acids are taken up on page 442. The disulfonic acids are secured by continued heating of naphthalene with concentrated sulfuric acid.

(4) *Nitronaphthalenes*. For the preparation of  $\alpha$ -nitronaphthalene see page 454.  $\beta$ -nitronaphthalene is made by nitration of  $\alpha$ -naphthylamine with dilute nitric acid:



followed by the elimination of the amino group by diazotization and treatment with alcohol (page 482); or it may be made by a modified Sandmeyer reaction from  $\beta$ -naphthylamine.

(5) *Naphthols*. For these see page 515. The sulfonic acids of the naphthols are important compounds in the dye industry, while several of the nitro derivatives are directly applied as dyes. These are Martius Yellow (Naphthalene Yellow) and Naphthol Yellow S. Martius Yellow is formed by direct nitration of  $\alpha$ -naphthol or naphthol mono- or disulfonic acid. Like picric acid this substance shows stronger acid properties than a phenol (naphthol). It decomposes alkaline carbonates and forms a salt with one equivalent of base. It dyes silk and wool yellow.

Martius  
yellowNaphthol  
yellow S

Naphthol Yellow S is made by nitration of  $\alpha$ -naphtholtrisulfonic acid, by which two nitro groups exchange for sulfo groups. It is a permitted food color and a better dye than Martius Yellow.

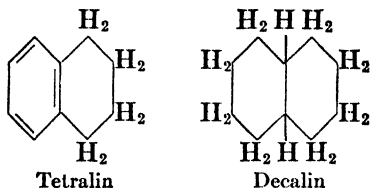
$\beta$ -Naphthol has a medical use as an intestinal antiseptic. Its methyl and ethyl ethers are employed in perfumery. Other derivatives, such as the benzoate and salicylate, are used in medicine.

(6) *Naphthylamines*. See page 476. Naphthylaminesulfonic acids are extensively used to form dyes. Direct treatment of  $\alpha$ -naphthylamine with concentrated sulfuric acid yields 1,4-naphthylaminesulfonic acid (naphthionic acid). This is used to make Congo Red (page 679).

(7) The *carboxy derivatives* of naphthalene are discussed on page 538.

(8) *Oxidation*. Chromic acid oxidation gives 1,4-naphthoquinone (page 565). Naphthalene heated to  $200^\circ$  with sulfuric acid, or to about  $500^\circ$  with air yields phthalic acid (page 535).

(9) *Reduction*. Naphthalene, reduced with sodium and alcohol, gives 1,4-dihydronaphthalene. When hydrogenated at  $200^\circ$ , ordinary pressure, with a nickel catalyst, tetrahydronaphthalene (tetralin) results. This compound is half aromatic, half aliphatic. It is used as a solvent. By more drastic hydrogenation, the aromatic ring is attacked to give decahydronaphthalene (decalin), also used as a solvent.



Tetralin with bromine gives a monobromo and dibromo derivative, in each case substituting on the alicyclic ring. On heating, these lose hydrogen bromide, to give respectively dihydronaphthalene and naphthalene. On this behavior is based the laboratory method of making hydrogen bromide by dropping bromine into boiling tetralin.

(10) *Metalation*. Naphthalene, dissolved in methyl ether or glycol dimethyl ether, and treated with sodium, forms a mono-sodium compound. The structure is not yet known. Biphenyl may also be metalated under the same conditions.

(11) With *picric acid*, naphthalene forms a yellow molecular compound which may be crystallized from alcohol. Its formula is  $C_{10}H_8 \cdot C_6H_2(NO_2)_3 \cdot OH$ . The melting point is  $150.5^\circ$ .

#### ANTHRACENE\*

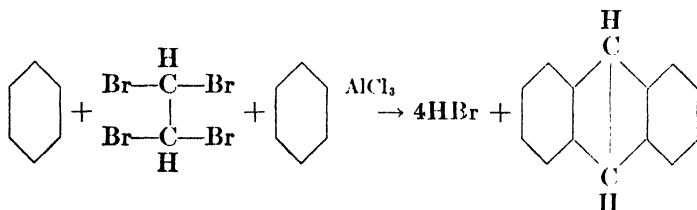
Anthracene,  $C_{14}H_{10}$ , which is found in coal tar in amount somewhat less than a half per cent, is isomeric with the hydrocarbon phenanthrene from the same source. It is used principally in the synthesis of anthraquinone and its derivatives.

\* Named from anthrax (Greek, = coal).

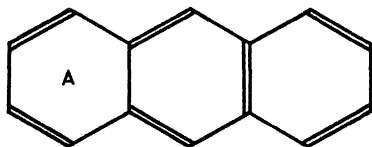
Anthracene occurs in colorless shining plates which have a blue fluorescence. It is but sparingly soluble in ether or alcohol, but dissolves in hot benzene. With picric acid a red crystalline compound is formed whose formula is  $C_{14}H_{10} \cdot C_6H_2(NO_2)_3 \cdot OH$ ; melting point,  $138^\circ$ .

The reactions of anthracene resemble those of the aromatic compounds benzene and naphthalene, which we have studied. It forms both addition and substitution products with the halogens according to the experimental conditions observed. Sulfuric acid yields mono- and disulfonic acids. Nitric acid, even when diluted does not, however, form a nitro compound. Instead, oxidation takes place forming anthraquinone.

**Structure.** The structure of anthracene is indicated by the methods which may be used in its synthesis. The compound may be formed by the action of aluminum chloride upon benzene and tetrabromoethane:



This synthesis seems to show that there should be a "para-bond" in the central ring of anthracene, and such a formula has been proposed and used. According to modern ideas the structure can best be shown as given below:

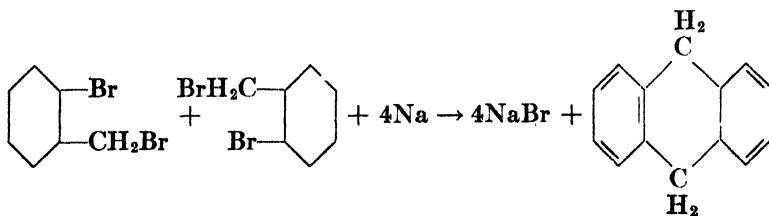


Anthracene

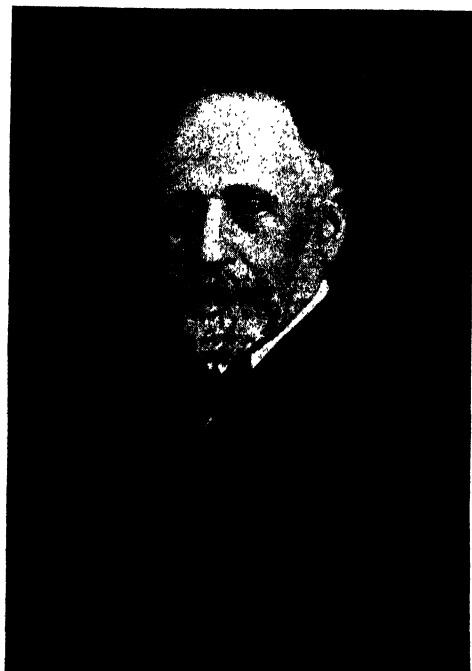
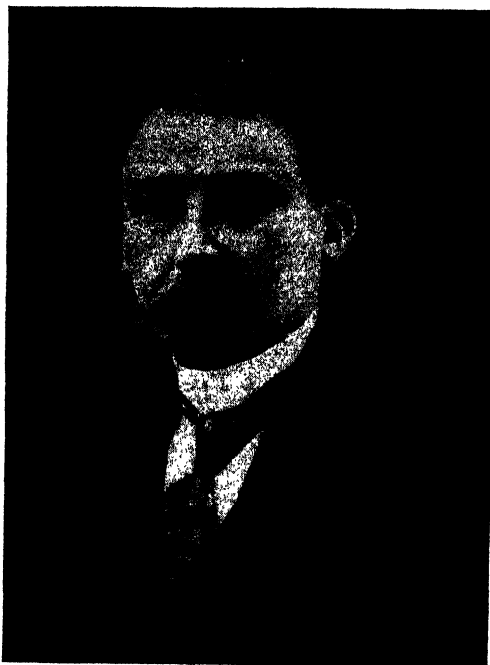
FIG. 89.

We will use the three-ring formula which omits the fourth valence of the carbon.

*o*-Bromobenzyl bromide when treated with sodium yields dihydroanthracene:

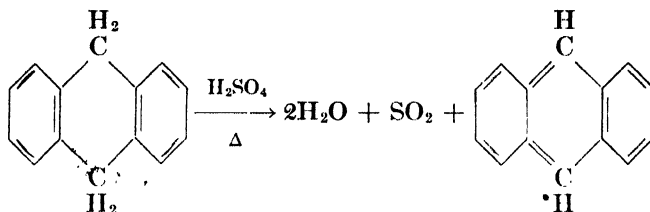


VICTOR GRIGNARD. (1871-1935, French.) His chief work was synthetic and his fame rests principally on the usefulness of the reaction which takes his name. A Nobel prizewinner in 1912. See *J. Chem. Education*, **7**, 1487 (1930); *J. Am. Chem. Soc.*, **59**, 17 (1937); *J. Chem. Soc. (London)*, **1937**, 171; also this book, pages 522, 569.

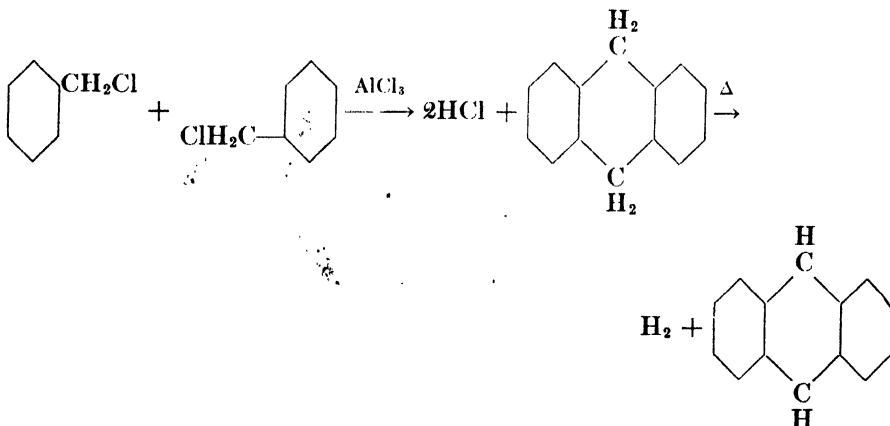


RICHARD WILLSTÄTTER. (German, 1872-1942.) A student and associate of Baeyer and later his successor at Munich. Studies of alkaloids (cocaine, atropine), quinones, flower pigments, catalytic hydrogenation, chemistry of enzymes. He is perhaps best known for his outstanding investigation of chlorophyll. He received the Nobel prize in 1915. See *Nature*, **120**, 1 (1927); *Ind. Eng. Chem.*, (News Edition) **20**, 954 (1942); *J. Am. Chem. Soc.*, **65**, 127 (1943); *J. Chem. Education*, **7**, 1984 (1930):

which is easily transformed to anthracene:

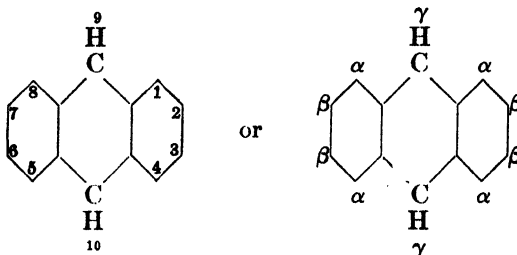


Benzyl chloride when treated with aluminum chloride also forms anthracene and other products.



These syntheses, and others which are known, show that in anthracene two benzene rings are joined to a third central ring by *ortho* carbon atoms. The central ring does not appear to have the benzenoid character, and it is more subject to attack by reagents than the outer rings.\*

**Numbering of Rings.** The numbering system used for anthracene is as follows:



by which it will be noted that there are three types of monosubstitution prod-

\* It is possible that the activity of carbons 9 and 10 is due to the *ortho* quinone structure of ring (A) (see Fig. 89).

ucts possible,  $\alpha$ -,  $\beta$ -, and  $\gamma$ -. With two like groups substituted for hydrogen, fifteen isomers are possible.

**Reactions.** The reactions of anthracene may be briefly outlined.

(1) *Halogenation.* Bromine in carbon disulfide forms anthracene dibromide, attaching to positions 9 and 10. This compound parts with HBr quite easily, forming in this way monobromoanthracene. Higher temperatures favor the formation of substitution products with the halogens. This substitution is so rapid that in the case of bromine the reaction may be satisfactorily used to prepare hydrogen bromide, by allowing bromine to fall dropwise upon anthracene.

(2) *Sulfuric acid*, when dilute, yields 1-anthracenesulfonic acid and 2-anthracenesulfonic acid. Concentrated acid gives 1,5- and 1,8-disulfonic acids. The reactions of these compounds are similar to those of the benzene-sulfonic acids.

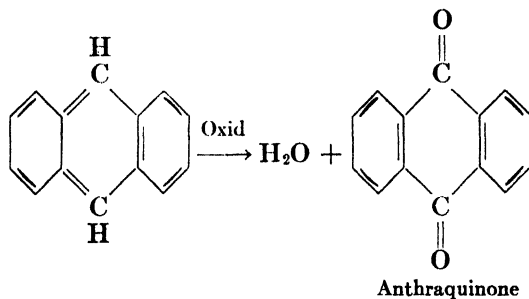
(3) *Nitric acid*, as has been stated, causes the oxidation of anthracene to anthraquinone. It is possible by indirect means to obtain both 9-nitroanthracene and 9,10-dinitroanthracene. The reduction of a nitroanthracene yields the corresponding aminoanthracene or anthramine.

(4) Both  $\alpha$ - and  $\beta$ -hydroxyanthracenes (called anthrols) are known. These behave like phenols or naphthols.

#### ANTHRAQUINONE

The most important derivative of anthracene is anthraquinone, which is easily formed by the oxidation of anthracene with chromic acid in glacial acetic acid solution. It is also formed when anthracene (with air) is passed over a heated catalyst.

A commercial method of preparation for anthraquinone, which may also be applied for the preparation of some of its derivatives, is given in method (2), page 594.

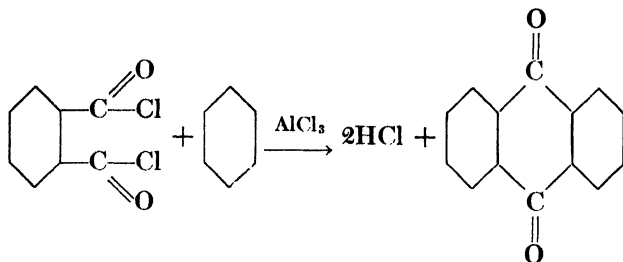


Anthraquinone occurs in yellow crystals; it is insoluble in water, and sparingly so in the majority of organic liquids. Either acetic acid or hot benzene is a satisfactory solvent. Anthraquinone sublimes upon being heated.

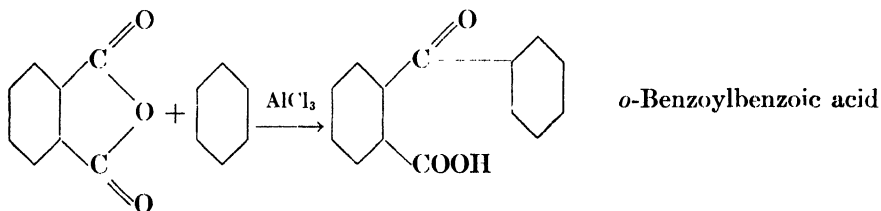


**Structure.** The structure of anthraquinone is established by several syntheses:\*

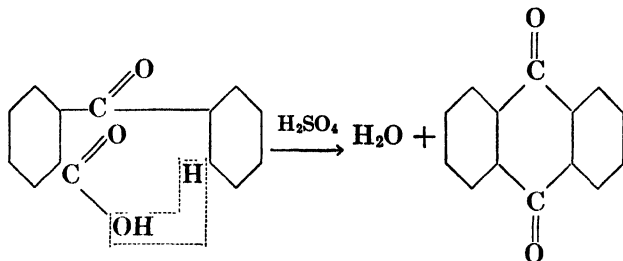
(1) From phthaloyl chloride and benzene:



(2) Phthalic anhydride and benzene, in the presence of aluminum chloride, condense giving *orthobenzoylbenzoic acid*:



Treatment with sulfuric acid causes the loss of water and formation of anthraquinone from the above compound:

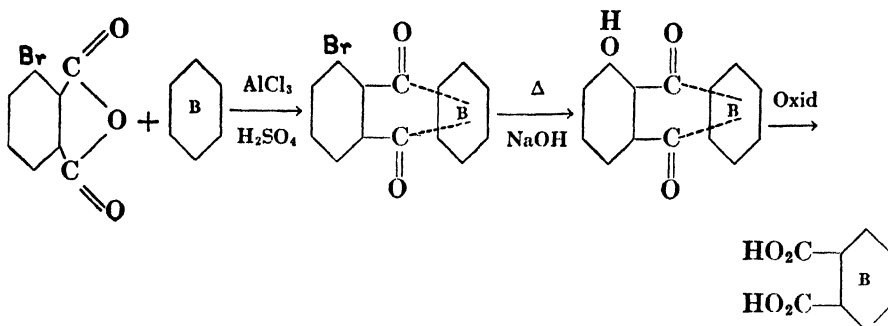


This synthesis gives a good yield of anthraquinone. It is important because it allows the preparation of derivatives of anthraquinone from substituted phthalic anhydride and substituted rings.

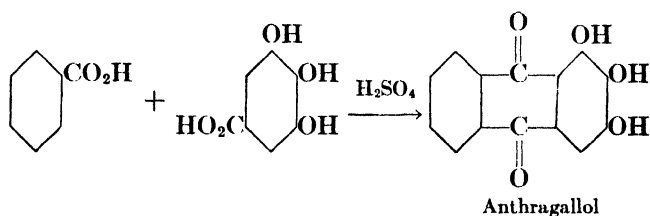
The synthesis also shows that anthraquinone has two benzene rings connected by two carbonyl groups, and that the carbonyl groups are *ortho* on one ring. To prove that the attachment on the other ring is also *ortho*,

\* Since anthraquinone may easily be reduced to anthracene, these syntheses constitute additional proofs of the structure of that compound.

we begin the synthesis with bromophthalic anhydride (or bromobenzoylbenzoic acid) as shown below in outline. The final compound is phthalic acid, hence the carbonyl groups are joined in *ortho* position on the second ring.

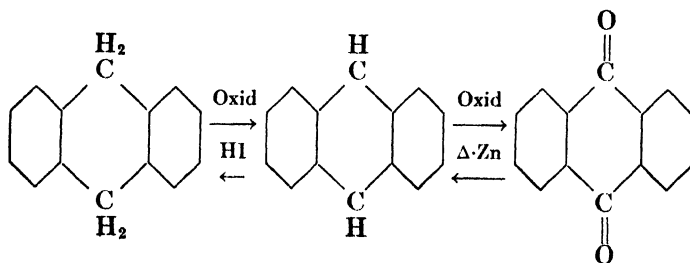


Another proof is afforded by the following synthesis of anthragallol:

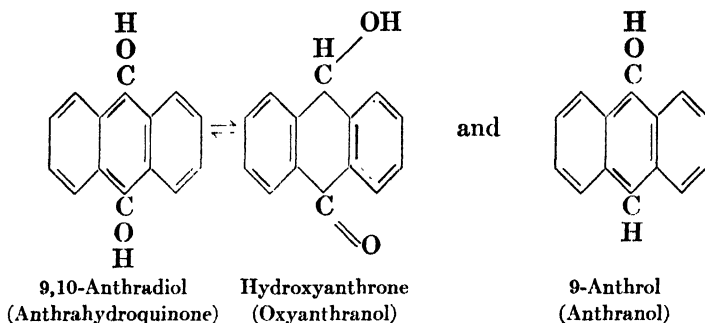


Other similar proofs could be given.

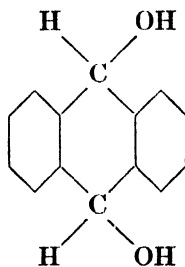
**Chemistry of Anthraquinone.** Anthracene, dihydroanthracene, and anthraquinone are related as shown below:



The name assigned to anthraquinone is in some respects deceptive, as this compound is in some physical aspects more like a ketone than a quinone. Thus it is odorless and is not exceptionally volatile nor highly colored, neither is it an effective oxidizing agent. The compounds produced upon careful reduction of anthraquinone are:



The latter compound is presumably formed by loss of water from:



Hydroxyanthrone dissolves in alkali giving a red solution. A test for anthraquinone and derivatives is based upon this reaction. When heated with zinc dust and dilute alkali, anthraquinone is reduced to hydroxyanthrone, and a deep red color appears. When the solution is exposed to air and shaken, the color fades, due to the reoxidation of hydroxyanthrone or the tautomeric compound, anthradiol, to anthraquinone.

Sulfonation of anthraquinone requires very concentrated acid and high temperature. The  $\beta$ -acid is the principal product. The use of mercury sulfate as a catalyst makes a profound alteration. The  $\alpha$ -acid is now the chief product, and the sulfonation is much more easily performed.

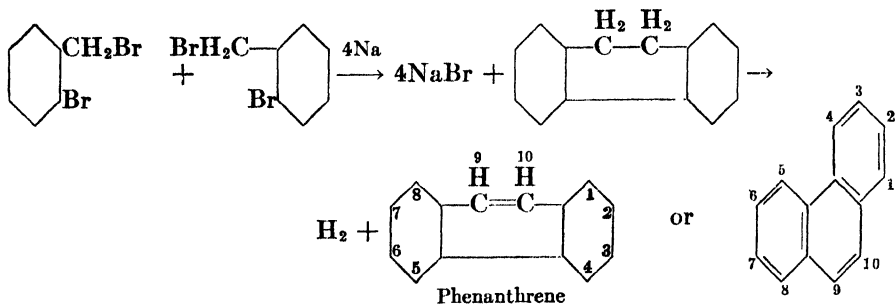
Alizarin is the most important of the derivatives of anthraquinone. This is discussed on page 692.

### PHENANTHRENE

As already stated phenanthrene,  $C_{14}H_{10}$ , and anthracene, also  $C_{14}H_{10}$ , occur together in one of the fractions taken in the distillation of coal tar. The former is removed from anthracene by the use of carbon disulfide or pyridine, in which it is more soluble than is anthracene.\* It is a colorless solid, insoluble in water, but soluble in alcohol or ether.

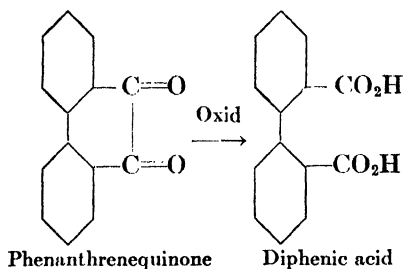
Phenanthrene is produced from the interaction of *o*-bromobenzyl bromide and sodium, a reaction which also yields anthracene, as we have noted:

\* Furfural may also be used for this separation.



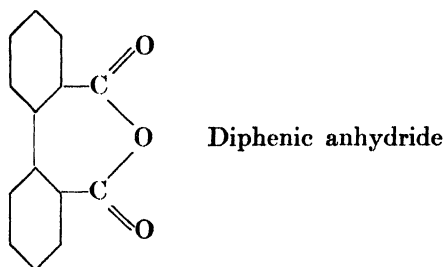
also when *o*-ditolyl is passed through a red-hot tube, phenanthrene results (see page 419). These and other syntheses establish the formula as presented above.

Oxidation of phenanthrene affects carbons 9 and 10 giving a diketone, phenanthrenequinone, which upon further oxidation yields diphenic acid.

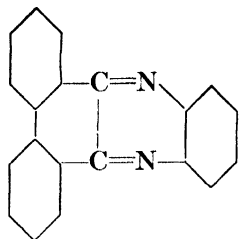


The first compound is perhaps misnamed. It differs from simple *para* quinones, being non-volatile and odorless. It forms a bisulfite compound and a dioxime.

It is interesting to note that diphenic acid forms an anhydride:



With *orthodiamines*, phenanthrenequinone reacts with loss of water to form yellow solids. Thus from *o*-phenylenediamine we get:



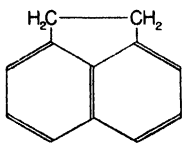
Dibenzo [a,c] phenazine

This reaction is not shown by *meta* or *para* diamines.

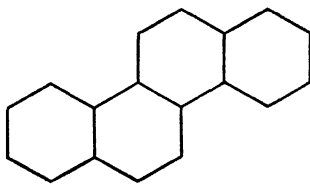
The hydroxy derivatives of phenanthrenequinone do not possess dyeing properties; hence neither this compound nor phenanthrene has the importance attaching to anthracene and anthraquinone.

### HYDROCARBONS WITH CONDENSED STRUCTURES

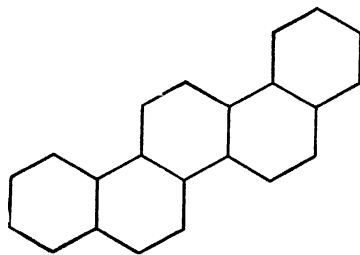
Other hydrocarbons present in coal tar which have condensed structures include the following:



Acenaphthene

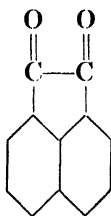


Chrysene



Picene

Acenaphthene may be synthesized by passing  $\alpha$ -ethylnaphthalene through a red-hot tube. Its oxidation yields 1,8-naphthalic acid (formula, page 538). Both oxidation and synthesis support the structure assigned to this compound, by which acenaphthene is seen to be a derivative of naphthalene. Oxidation of acenaphthene yields as an intermediate compound, the ketone, acenaphthenequinone:

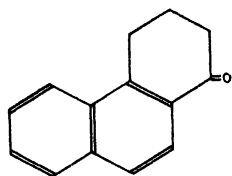


Acenaphthenequinone

### THE PHENANTHRENE NUCLEUS

Though phenanthrene is uninteresting from the standpoint of dye production, its derivatives have a tremendous biological importance. The phenanthrene nucleus is found in morphine alkaloids (morphine,

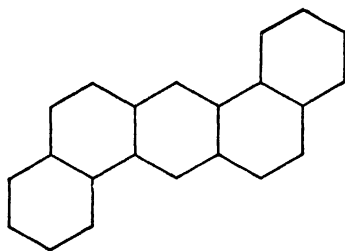
codeine), in cholesterol and ergosterol (thus also in vitamin D), in the sex hormones (see page 743), and in many other compounds of biological significance. In view of this likeness in structure we should not be surprised to find a corresponding similarity in function. To some extent this is true. For instance, certain phenanthrene derivatives are definitely estrogenic. Compound (I) below has this action, while certain derivatives of (II) are more active than estriol.



1-Ketotetrahydro-  
phenanthrene

(I)

FIG. 90.



1,2,5,6-Dibenzanthracene

(II)

FIG. 91.

#### CANCER-PRODUCING HYDROCARBONS

It has been known for some time that workers engaged in processing coal tar were apt to have skin cancer. That something in the tar was responsible for this was established by experiments in which rabbits and mice were treated with tar, and later with definite hydrocarbons, of which 1,2-benzopyrene and methylcholanthrene may serve as examples.

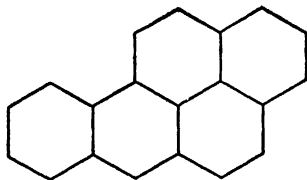


FIG. 92.—1,2-Benzopyrene.

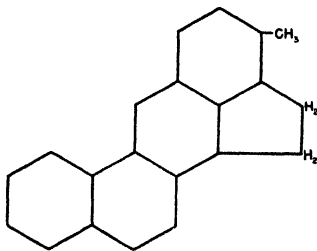


FIG. 93.—Methylcholanthrene.

Contact with hydrocarbons of this type produces skin cancer and injection gives internal cancer. The significance of this discovery can be appreciated. Now the fact that the sex hormones, cholesterol, and other compounds in the body, have a skeleton structure similar to that of methylcholanthrene makes it at least possible that the carcinogenic hydrocarbons may be formed in the body from the sex hormones, etc.\*

\* Other unrelated hydrocarbons (tetraphenylmethane) are reported to be carcinogenic, also non-hydrocarbons, as 2-amino-5-azotoluene.

Cancer has actually been produced in mice by injection of estrone benzoate. Further research of the cancer problem along the lines indicated will undoubtedly lead to valuable discoveries.

### REVIEW QUESTIONS

- Write graphic formulas for the following. (a) 1-Naphthol-3,6-disulfonic acid; (b) Naphthalene tetrabromide; (c) Martius yellow; (d) Decalin; (e) 1-Chloro-3,6-dinitroanthracene; (f) 2,3-Dichlorophenanthrenequinone; (g) Anthrahydroquinone.
- What compounds would be formed by reaction of the following compounds?
  - $\alpha$ -Naphthylamine and dilute  $\text{HNO}_3$ ;
  - Anthracene and picric acid;
  - sym*-Tetrabromoethane, benzene, and aluminum chloride;
  - o*-Benzoylbenzoic acid and  $\text{H}_2\text{SO}_4$ ;
  - Benzyl chloride and  $\text{AlCl}_3$ ;
  - Benzoic acid, gallic acid, and  $\text{H}_2\text{SO}_4$
- Write formulas for all possible dichloronaphthalenes; name the compounds. Do the same for the nitrodichloronaphthalenes.
- Suggest methods for making: (a) 1-Anthracenesulfonic acid; (b) Naphthalene tetrachloride; (c)  $\beta$ -Naphthalenesulfonic acid; (d) Diphenic anhydride.
- Write equations for the formation of the following derivatives of naphthalene: (a)  $\alpha$ -Naphthalenesulfonic acid; (b)  $\beta$ -Nitronaphthalene; (c)  $\alpha$ -Naphthylamine; (d)  $\beta$ -Naphthol; (e)  $\alpha$ -Naphthoic acid.
- Write equations showing what substances would probably be formed in the following reactions: (a) Sodium salt of  $\beta$ -naphthol with ethyl iodide; (b) Naphthalic anhydride and phenol; (c)  $\alpha$ -Naphthalenesulfonic acid salt and sodium formate (fusion); (d)  $\alpha$ -Naphthoquinone and  $\text{NH}_2\text{OH}$ .
- Give equations for three methods of synthesizing anthracene.
- Write equations for the reaction of the following compounds with anthracene: (a)  $\text{HNO}_3$ ; (b)  $\text{Br}_2$ ; (c) Dilute, and concentrated sulfuric acid.
- Write equations for two methods by which anthraquinone may be made.
- Write equations for the synthesis of phenanthrene (two methods).
- Write equations for the probable course of the reaction between: (a) Phenanthrenequinone and  $\text{NH}_2\text{OH}$ ; (b) Diphenic anhydride and  $\text{NH}_3$ ; (c) Acenaphthenequinone and phenol.
- Write equations for the synthesis of acenaphthene and acenaphthenequinone.
- Which is more acidic, *ac*-tetrahydronaphthol, or *ar*-tetrahydronaphthol?
- Of the two types of tetrahydronaphthylamines, which should be more basic? Which should have the higher boiling point?
- Anthracene may be made by distillation of phenyl-*o*-tolyl ketone with zinc dust. Discuss this synthesis and its relation to the assigned structure of anthracene.
- Decalin occurs in *cis* and *trans* forms. Sketch the graphic formula for each of these forms.
- What naphthalene derivative should be formed by the oxidation of acenaphthenequinone? How would the new substance react with a dehydrating agent?
- When *o*-methylbenzophenone is heated with zinc dust, one of the hydrocarbons discussed in this chapter results. Which one? Which formula of the hydrocarbon is upheld by this synthesis?
- Write graphic formulas showing the necessary arrangement of bonds in the rings of 9, 10-anthradiol and oxyanthranol.
- What peculiarity of structure is noted in diphenic anhydride?
- Give valid proofs of the correctness of the naphthalene structure.
- Cite syntheses which support the anthracene structure.
- How would you synthesize 6-chloroanthraquinone?

24. The distillate of calcium salts yields ketones. What calcium salt upon such treatment would give anthraquinone as a product?
25. The organic compound (A) contains 59.80% C, 3.56% H, and 25.27% Cl; the balance is oxygen. (A) reacts with hydroxylamine and with phenylhydrazine. The compound formed with hydroxylamine contains 4.73% of N. Mild oxidation of (A) gives (B) which contains 60.20% C, 2.87% H, and 25.45% Cl; the balance is oxygen. Vigorous oxidation of (A) gives (C) which contains 53.67% C, 3.20% H, and 20.45% O; the balance is Cl. (C) is an acid; 10.87 cc. of 0.092 N KOH solution is exactly neutralized by 0.1565 g. of the compound. (C) melts at 242-3°C. Treatment of (A) with an acetylating agent gives a new compound containing 59.44% C, 3.72% H, and 14.86% O; the balance is Cl. Prove the structure of (A) and show how to make it from benzene.

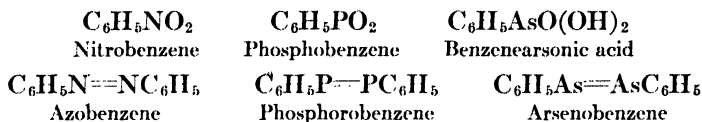
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AROMATIC ARSENIC, PHOSPHORUS, ANTIMONY, AND  
MERCURY COMPOUNDS

Certain analogies exist between aromatic compounds of arsenic and phosphorus, and the nitrogen compounds already discussed in this book. This will be noted from an inspection of the following formulas and equations:

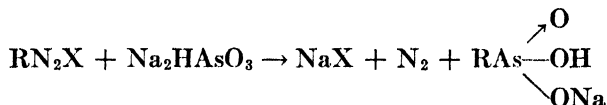


(a) Nitration of aniline with nitric acid to yield *p*-nitroaniline,  $\text{H}_2\text{NC}_6\text{H}_4\text{NO}_2(p)$ .

(b) Sulfonation of aniline with sulfuric acid to yield *p*-sulfanilic acid,  $\text{H}_2\text{NC}_6\text{H}_4\text{SO}_3\text{H}(p)$ .

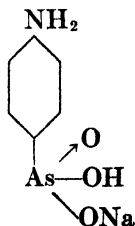
(c) Arsonation of aniline with arsenic acid to yield *p*-arsanilic acid,  $\text{H}_2\text{NC}_6\text{H}_4\text{AsO}(\text{OH})_2(p)$ .

Derivatives of arsenic acid may be prepared directly from the acid if amino or hydroxyl group is present on the ring. For example, *p*-arsanilic acid may be made as indicated above by heating aniline with arsenic acid to about  $160^\circ$  for some hours. Direct arsonation is seen to be more difficult than nitration. The **Bart reaction** also offers a means of introducing this group into the benzene ring. In this method a diazotized amine is treated with sodium arsenite, and warmed to drive off nitrogen.



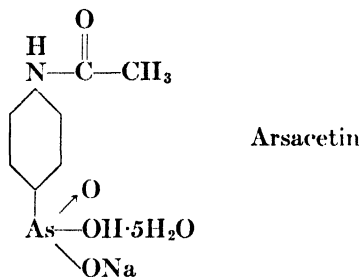
Arsenobenzene may be made by the reduction of benzenearsonic acid  $\text{C}_6\text{H}_5\text{AsO}(\text{OH})_2$ , and in other ways.

**Curative Compounds.** Great interest has been shown in the organic derivatives of arsenic, since the definite proof in 1905 that atoxyl has a curative effect in trypanosomiasis. Today, literally thousands of these compounds are known, all of them being of synthetic production. Among the early arsenicals is **atoxyl**, the sodium salt of arsanilic acid:

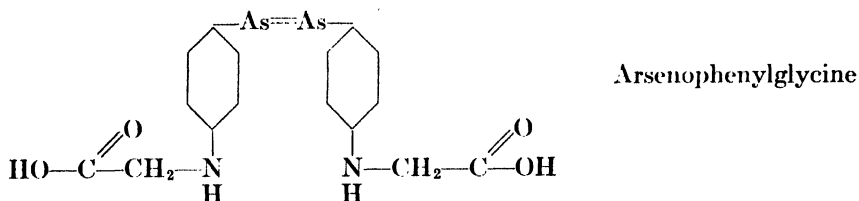


Atoxyl (Discovered 1863 by Béchamp)

This compound was used as a remedy for sleeping sickness, but, like arsacetin it is toxic, causing blindness in certain cases.

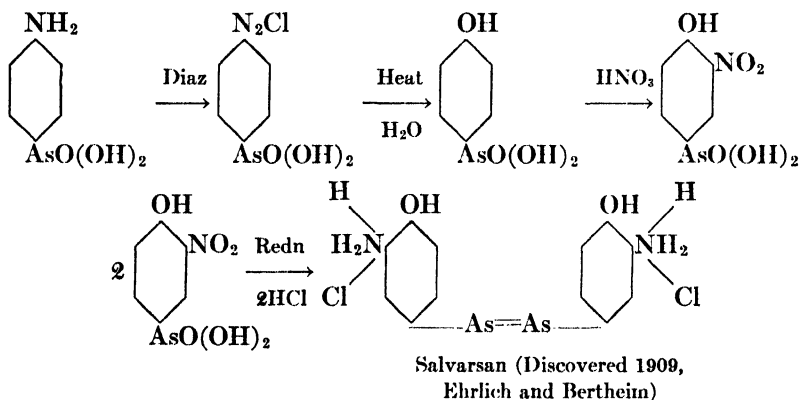


Later, **arsenophenyglycine**, a yet more effective remedy was introduced:



The research of Ehrlich demonstrated that compounds containing the group  $\text{—As=As—}$ , found in arsenobenzene, had a higher curative value in combating trypanosomes than compounds like atoxyl. The culmination of this research was the preparation of **Salvarsan**, “606,”\* or Arsphenamine, which has proved its value in the treatment of spirochetal infections, particularly syphilis (1910).

A method of synthesis of salvarsan is as shown below:

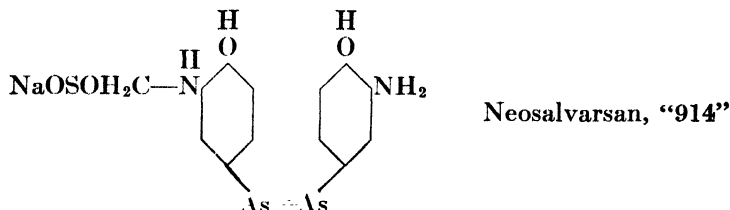


The synthesis may begin with *p*-hydroxyphenylarsonic acid, made by the direct arsonation of phenol.

\* This was the 606th preparation made in the investigation.

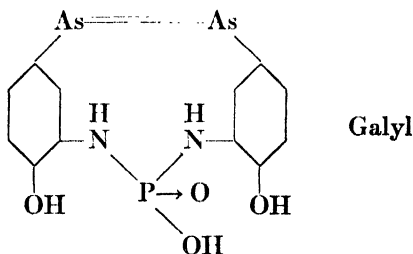
When alkali is added to a solution of arsphenamine, the free base is precipitated; further addition of alkali produces a monosodium salt, which is soluble in water, finally a disodium salt, by attacking the phenol groups. Solutions of the disodium salt, made from the dihydrochloride, are commonly used in treatment. They are quite alkaline.

The use of the base is necessary; salvarsan is too acid to be used directly. **Neosalvarsan**, like salvarsan and its sodium salts, is water-soluble; it gives a neutral solution and can be used directly.



Neosalvarsan while not as effective therapeutically as salvarsan is better tolerated by patients and has a lower toxicity than has salvarsan.\*

Derivatives of salvarsan which have therapeutic value include **Galyl**:

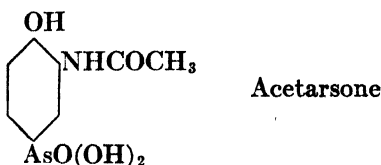


and **Sulpharsphenamine**, prepared from salvarsan by treatment with formaldehyde and sodium bisulfite:



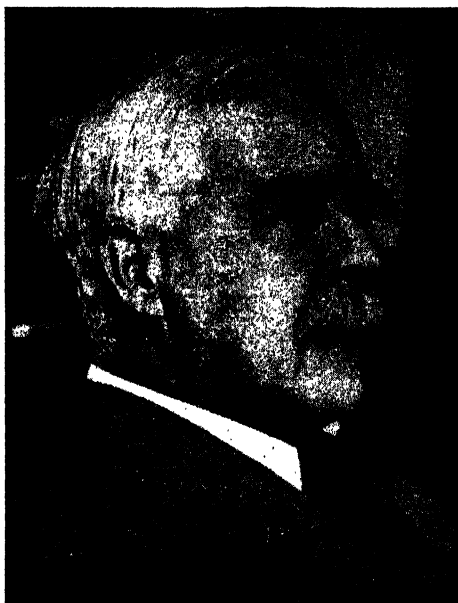
Sulpharsphenamine, unlike arsphenamine, may be used for intramuscular injection.

**Silver arsphenamine**, which contains combined silver oxide, has certain advantages over other arsphenamines. **Acetarzone**, **Stovarsol**, has the advantage that it may be given orally. It has been used in the treatment of amebiasis.



\* Some idea of the importance of salvarsan and neosalvarsan may be gained from the U.S. sales in 1940 which were about one million dollars.

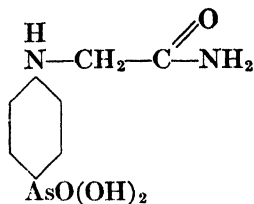
GILBERT N. LEWIS. (American, 1875-1946.) Lewis was primarily a physical chemist. Organic chemists are immensely indebted to him for the concepts of valence and atomic structure which he has given them. His book on "Valence" has given great impetus to research and has been of equal value in the teaching of organic chemistry. Formerly dean of the College of Chemistry in the University of California; see page 229.



*Wide World Studio.*

JAMES COLQUHOUN IRVINE. (British, 1877-- .) Irvine's chief interest is in the field of carbohydrates (determination of structure of polysaccharides, chemistry of cellulose, inulin, starch, monosaccharides). He is now the principal and vice-chancellor of the University at St. Andrews, Scotland.

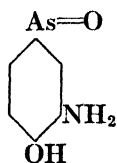
**Tryparsamide** is a derivative of atoxyl, formed through action with chloroacetamide:



Tryparsamide  
(Jacobs and  
Heidelberger,  
1919)

It is used with success for African sleeping sickness and in the treatment of neurosyphilis.

Since it appears highly probable that the arsphenamines do not exert a direct action, but act through oxidation compounds which are arsenoxides, the use of "arsenoxide" or **Mapharsen** has been introduced (1934).



Mapharsen (Discovered 1908), (*meta*-amino-*para*-hydroxy-phenyl-arsine-oxide).

Mapharsen acts more promptly and is less toxic than arsphenamine, and is given in a smaller dose. It is stable to air, in contradistinction to arsphenamine. It is estimated that more than 12 million doses of this drug were administered in the period 1932-1942.

**War Gases.** The toxic nature of arsenic compounds has led to their use as poisons. In this connection mention should be made of Lewisite, and other aliphatic compounds shown on page 323. In the first World War diphenylchloroarsine,  $(\text{C}_6\text{H}_5)_2\text{AsCl}$ , was employed as a "snecze gas." Other aromatic substances used as war gases include phenylcarbylamine chloride,  $\text{C}_6\text{H}_5\text{NCCl}_2$ ; phenyldibromoarsine,  $\text{C}_6\text{H}_5\text{AsBr}_2$ ; diphenylcyanoarsine,  $(\text{C}_6\text{H}_5)_2\text{AsCN}$ ; diphenylaminechloroarsine,  $\text{HN}(\text{C}_6\text{H}_4)_2\text{AsCl}$  (Adam-site); phenyldichloroarsine,  $\text{C}_6\text{H}_5\text{AsCl}_2$ ; xylol bromide,  $\text{CH}_3\text{C}_6\text{H}_4\text{CH}_2\text{Br}$ ; benzyl bromide,  $\text{C}_6\text{H}_5\text{CH}_2\text{Br}$ ; brombenzyl cyanide,  $\text{C}_6\text{H}_5\text{CHBrCN}$ ; chloroacetophenone,  $\text{C}_6\text{H}_5\text{COCH}_2\text{Cl}$ .

## ANTIMONY

The use of organic antimony compounds in the treatment of human ailments dates from a period prior to the 17th century. A well known antimony compound at the time was tartar emetic, potassium antimonyl tartrate (formula, page 265), which is still employed as an expectorant.

In 1908, the discovery was announced that mice infected with trypanosomiasis were greatly helped by injections of tartar emetic. This announcement, as well as the success of the arsenicals in the treatment of diseases caused by protozoan parasites, has stimulated research in the field of anti-

monials. The antimony compounds have not so far been studied as extensively as have the arsenicals, but they hold great promise. Apparently, there are cases where antimony compounds are much more effective than arsenic derivatives.

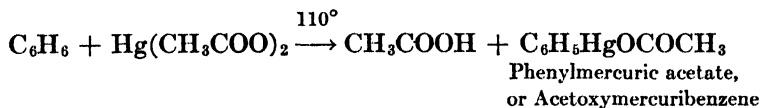
Schistosomiasis, a disease of parasitic origin known in Egypt, China, and South Africa, has been successfully attacked with antimonials, also the Leishmanioses, common in India and China. The transmission of trypanosomiasis is commonly effected through the bite of insects (in Africa the tsetse fly). Where cattle are to be driven across a region infested with these insects, they may be given a temporary immunity to infection by the use of antimony compounds.

Antimony compounds with the groups,  $-\text{ArSb}=\text{SbAr}-$ , have been prepared (Stibino compounds). It will be recalled that the arseno compounds are markedly effective arsenicals. Also, arseno-stibino compounds,  $-\text{ArAs}=\text{SbAr}-$ , have been made. Both of the above illustrated types have notable trypanocidal powers. For formulas and pharmacological data, see References 10 and 11, page 608.

## MERCURY

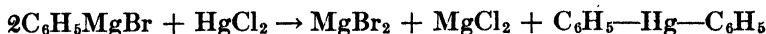
Organic compounds of mercury have been made and studied since about 1850, and a very large literature has collected bearing on these compounds and their reactions, probably as large as that devoted to the arsenic compounds, or larger. Interest now attaches to these compounds because of the bactericidal action which is shown by many of them; hence their use as external and internal antiseptics, and in the treatment of syphilis, etc.

The mercuration of an aromatic compound is a general reaction, like sulfonation or nitration. One method of introducing the mercury atom is by the use of mercuric acetate. With benzene we get phenylmercuric acetate:



Toluene, aniline, or phenol treated with the same reagent are mercurated in the *para* and *ortho* positions; nitrobenzene, which usually gives *meta* products, is also mercurated, mainly in the *ortho* position.

The Grignard reagent may be used to form diphenylmercury:



Other methods are known by which mercury compounds may be formed; the formation of dialkyl mercury compounds is illustrated on page 325.

**Curative Compounds.** Organic mercury compounds used in medicine include the following:

*Mercurochrome-220*, dibromo-hydroxymercuri-fluorescein. This is well established as a urinary antiseptic; it is also used as a surface antiseptic.

*Mercurosal*, disodium-hydroxymercuri-salicyloxy-acetate,



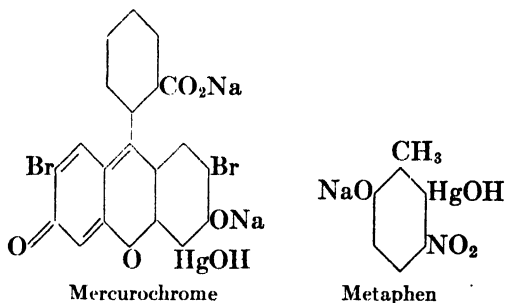
is used in the treatment of syphilis.

*Metaphan*, 2-Hydroxymercuri-3-nitro-6-hydroxytoluene (sodium salt). This is a very powerful germicide, especially against staphylococci. It is non-irritative to skin and mucous membrane, and does not tarnish surgical instruments. The compound has a powerful spirocheticidal action.

*Merthiolate*, sodium ethylmercurithiosalicylate. Germicide, reported stable in presence of protein material, as blood serum.

*Meroxyl*, sodium salt of 2,4-dihydroxy-3,5-dihydroxymercuribenzo-phenone-2'-sulfonic acid (antiseptic, gonorrhea).

*Mercury oleate* (skin diseases, syphilis), *mercury salicylate* (syphilis, antisepsis), *mercury succinimide* (antiseptic, antisyphilitic), and *mercury benzoate* (syphilis) are organic salts useful in the treatment of diseases as indicated herewith.



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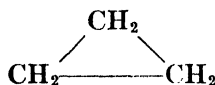
## CHAPTER XXXII

### ALICYCLIC COMPOUNDS

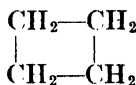
The ring compounds so far considered have either been of aromatic type, or have been easily hydrolyzable aliphatic ring compounds with at least one foreign atom in the ring. Acid anhydrides would fall in this latter class.

The alicyclic compounds are derived from ring paraffins. Every normal alkane save methane and ethane could, at least in theory, have an alicyclic counterpart, which would be made (theoretically) by removing hydrogen at each end of the normal chain and joining the ends to form a ring. The formula of an alicyclic hydrocarbon would then be  $C_nH_{2n}$ ; evidently these are isomeric with the olefins.

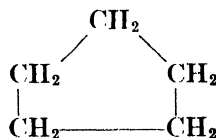
The class name for the saturated hydrocarbons is cycloalkanes or cycloparaffins or polymethylenes. Individual members take the aliphatic name with the prefix "cyclo," thus:



Cyclopropane



Cyclobutane



Cyclopentane

These three compounds do not show the same chemical behavior, thus cyclopropane with HBr gives *n*-propyl bromide, but cyclopentane does not react. The Baeyer strain theory was offered to explain the difference in ease of formation and in the stability of rings of different sizes.

#### BAEYER STRAIN THEORY

Like the van't Hoff theory, that of Baeyer sets out from the tetrahedral carbon atom (page 333). It will be remembered that the angle between the valence bonds of the carbon atom is  $109^{\circ}28'$ . If two carbons are joined, as in ethane, the skeleton structure diagram will be as shown in Fig. 94.

Consider the compound ethylene. If ethylene is to have two parallel bonds joining the carbon atoms, then bonds (1) and (2), Fig. 95 must be bent inwards toward each other over  $50^{\circ}$  of arc ( $54^{\circ}44'$ ). This implies a condition of great strain. We may use this conception to explain the addition reactions of ethylene. In the strained formula of ethylene the shared electron pairs cannot all at the same time assume the most favorable position.

When three carbons are joined together, the ends of the bonds of carbons #1 and #3 approach each other somewhat, as shown in Fig. 96.\* Still, in order to form a ring compound it would be necessary to bend the bonds inward to a certain extent ( $24^{\circ}44'$ ). When four carbons are joined in a

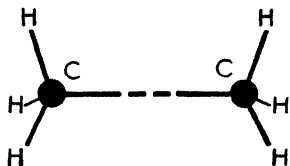


FIG. 94.

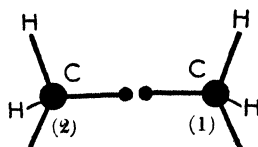


FIG. 95.

ring this amount of bending is only  $9^{\circ}44'$ , and for a ring of five carbons the amount of bending decreases to  $0^{\circ}44'$ .

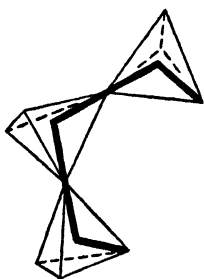


FIG. 96.—Three-atom chain.

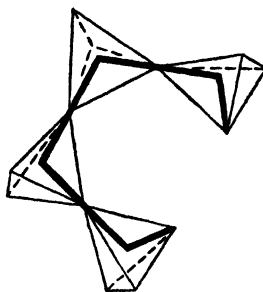


FIG. 97.—Four-atom chain.

Hence the five-atom ring compounds are not only formed with ease but are stable, with practically no tendency to disrupt the ring. In a six-atom ring the "strain" is  $-5^{\circ}16'$  (outwards).

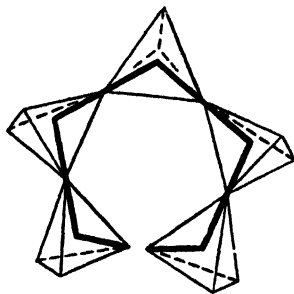


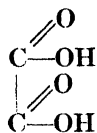
FIG. 98.—Five-atom chain.

This theory accounts for the easy formation of ring compounds by such substances as phthalic acid, succinic acid, and  $\gamma$ -hydroxybutyric acid, and for the failure of such substances as oxalic acid and malonic acid to form anhydrides. Groups on the ends of a five- or six-atom chain are seen

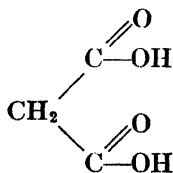
\* Note also Fig. 13, page 39.

to be within easy reach of each other, and reactions can take place between them under these conditions, which would be difficult or impossible if a greater separation existed.

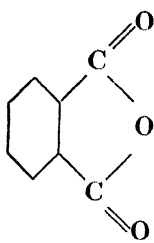
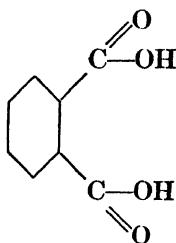
**Applications of the Theory.** The following examples show the working out of this theory when applied to anhydride formation:



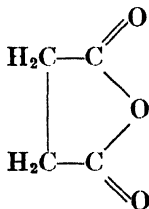
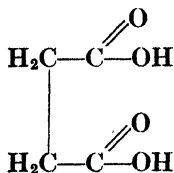
Oxalic acid. Does not form anhydride. Ring of three.



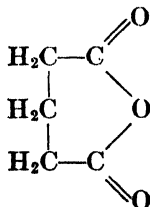
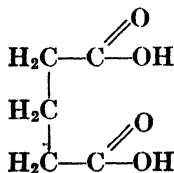
Malonic acid. Does not form a monomeric anhydride. Ring of four.



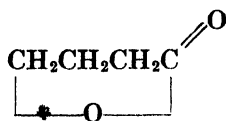
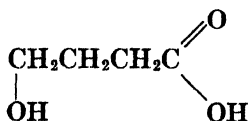
Phthalic acid. Forms anhydride. Ring of five.\*



Succinic acid. Forms anhydride. Ring of five.

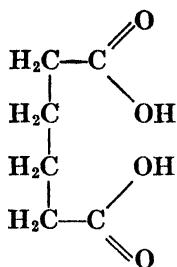


Glutaric acid. Forms anhydride. Ring of six.



$\gamma$ -Hydroxybutyric acid. Forms lactone. Ring of five.

\* The inclusion of oxygen in these rings does not affect the theory, as the valence angle of the oxygen cannot differ much from that of carbon.



Adipic acid. Ring of seven. Forms anhydride which easily polymerizes. See page 255.

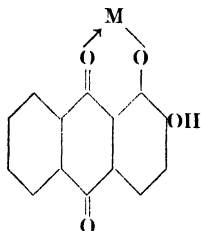
**Exceptions to the Theory.** Although this theory is meant to apply to cycloparaffins, and meets with exceptions when generally applied, it is nevertheless useful in predicting possible reactions of other types of compounds. Also it is evident that five- and six-atom ring structures predominate in the naturally occurring organic compounds and are most easily prepared in the laboratory, both of which facts are rendered logical by this theory. There are, however, several points which the theory does not cover. It is expressly implied that large rings would be formed with difficulty and that they would be unstable, but the latter point has been disproved by the recent work of many investigators. Cyclic ketones having up to thirty carbons in their rings have been made, cyclic hydrocarbons with as many as thirty members in the ring, and heterocyclic compounds with large rings. None of these compounds was inherently unstable. The yields in such syntheses are small and it is easy to see why this is so. A ring can form only when the ends of a chain approach each other closely, and with chains of five and six members this will often occur. Free rotation is possible with each carbon-to-carbon bond, but in a chain of five members there are only four bonds between carbons. As the length of a chain increases, the possibilities for the chain to assume various forms by free rotation at the bonds become much more numerous, and it is only seldom that the molecule assumes just the right conformation for the building of a ring.

If these large rings were built in one plane as the Baeyer theory assumes, they would be quite unstable, but as experience shows that they are stable, the rings must be multiplanar. They are known as *strainless rings*. A few experiments with the wire atomic models will show that it is natural for rings of three to five carbon atoms to lie in one plane, but that rings of six carbons and larger naturally lie in more than one plane. The theory of multiplanar rings, due to Sachse and Mohr, applies, then, to rings having more than five members. Many interesting developments have come from it. To take a simple case, the theory predicts that decahydronaphthalene should exist in two forms, *cis* and *trans* as shown in Figs. 99 and 100. These compounds and others with the same kind of isomerism have been made. X-ray studies have confirmed the purely chemical evidence cited here.



disposition of electrons; in other words the compound displays resonance. The chelate ring of acetoacetic ester is of the type most commonly found (six atoms and two double bonds).

The insoluble lakes formed by acid dyes and metallic mordants (page 676) may also have chelation, and this seems highly probable upon consideration of the dye structures which will and will not form lakes. Alizarin easily forms such lakes with aluminum, iron, and chromium salts. A chelate compound of the metal and alizarin would have six-atom rings:

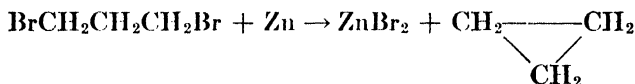


Alizarin lake (M = metal)

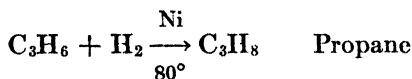
#### METHODS OF RING FORMATION,\* CYCLOALKANES

Several methods of ring closure will be presented together with a discussion of some of the cycloalkanes.

##### (1) Use of the Freund Reaction. Cyclopropane.†



Cyclopropane is a gas which has considerable value as an inhalation anesthetic, particularly as a preliminary to ether. The ring "strain" is revealed by the reactions with hydrogen, hydrogen bromide, bromine. In each case the ring opens and the reaction really resembles an olefin addition.‡

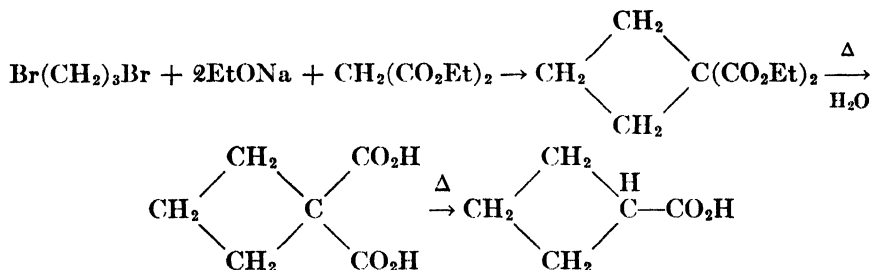


\* Ring closures which produce rings with a foreign atom (heterocyclic rings) have been shown in connection with the anhydrides, page 254, imides, page 255, lactones, page 241, lactides, page 240, pyrazolone, page 644, lactams, page 245, furaldehyde, page 641, and will appear in Chapter XXXIV.

† When Carothers and co-workers attempted this reaction with decamethylene bromide,  $\text{Br}(\text{CH}_2)_{10}\text{Br}$ , polymers were obtained with 20, 30, 40, 50, 60, 70 and even more carbon atoms united. They were open-chain compounds.

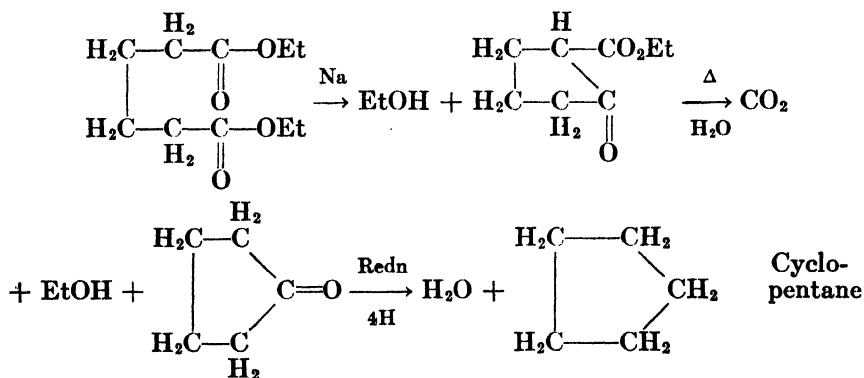
‡ See for example, *J. Am. Chem. Soc.*, **60**, 577 (1938).

## (2) Use of Malonic Ester. Cyclobutane.



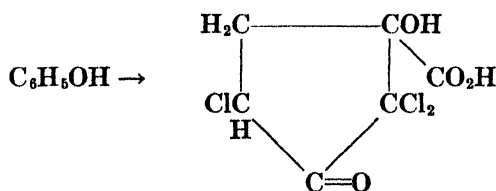
Cyclobutane can be made from the carboxylic acid above by a roundabout process. Its physical properties are like those of cyclopropane. When treated with hydrogen at 120° (nickel catalyst) butane results. The higher temperature required indicates an increasing ring stability over that of cyclopropane.

## (3) Intramolecular Acetoacetic Ester Condensation. Cyclopentane.

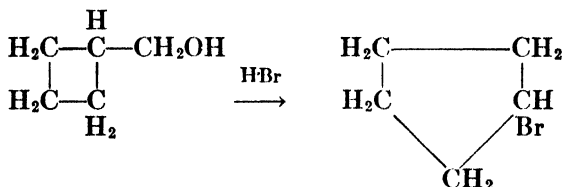


Cyclopentane reacts with bromine by substitution. The ring may be opened by treatment with hydrogen and a platinum catalyst, but only at 300°C. These facts show the stability of the 5-atom ring. Further illustrations of this stability are found in the following reactions.

a. Treatment of phenol with chlorine and alkali gives a 5-atom ring:



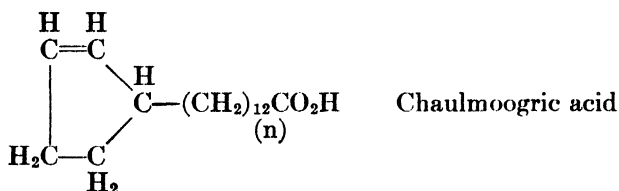
b. Cyclobutylcarbinol with hydrogen bromide gives a 5-atom ring:



c. When pinene is treated with hydrogen chloride a shift takes place which changes a 4-atom ring to a 5-atom ring (page 633).

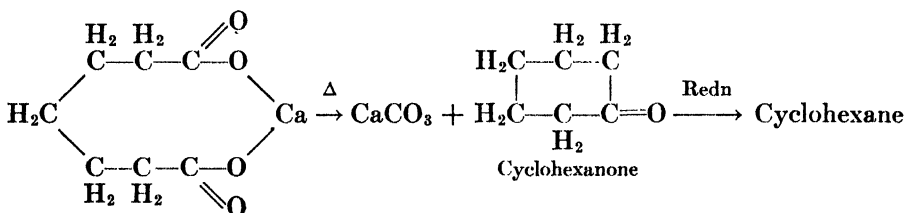
Many 5- and 6-membered alicyclic compounds are found in plants and in petroleum. The terpenes and camphors are for the most part alicyclic. Alicyclic hydrocarbons of petroleum are termed "naphthenes."

Important natural representatives of 5-atom rings are chaulmoogric acid and hydnocarpic acid, the chief components of chaulmoogra oil, used to treat leprosy.



The ethyl esters are also used. In hydnocarpic acid the structure is the same, but  $n = 10$ .

#### (4) Heating of Cyclic Calcium Salts. Cyclohexane.

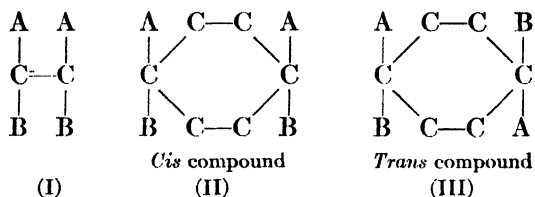


Cyclohexane is easily made from benzene by heating with hydrogen (nickel) to  $200^\circ$ . Conversely, heating cyclohexane to high temperature with platinum gives benzene. There is a very close relationship between the derivatives of benzene and of cyclohexane, and there are many instances in which an alicyclic compound can easily be changed to benzene type or vice versa. (Note tautomerism of phloroglucinol, page 515.)

Two six-atom compounds which are now being made commercially are cyclohexylamine and dicyclohexylamine. They are finding a number of uses which depend upon their basicity and their solvent powers.

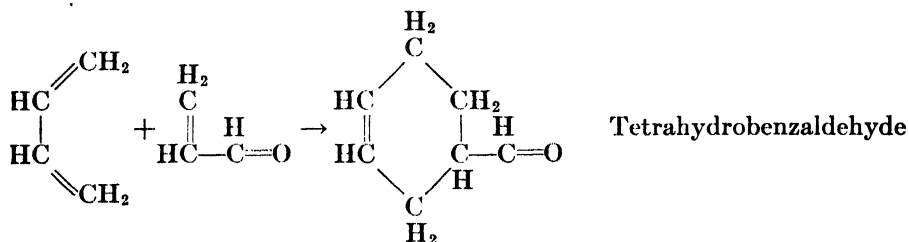


**Isomerism of Ring Compounds.** In the alicyclic compounds we observe a *cis-trans* isomerism which proceeds from the same cause as that observed with ethylene compounds. That is to say, the two sides of the ring in II act like the double bond in I and prevent free rotation. In this way isomers like II and III arise.

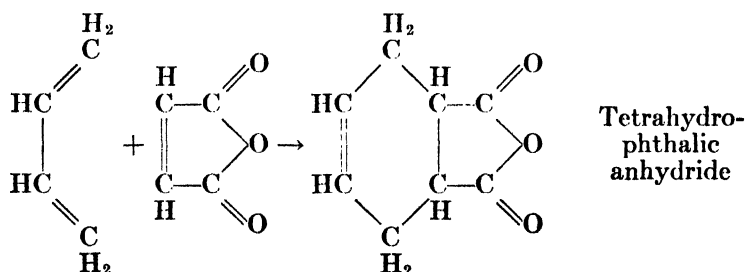


Unsaturated alicyclic compounds have considerable interest but cannot be discussed at length. The terpenes offer examples of such derivatives. A very important method of making certain cyclohexene derivatives is offered by the Diels-Alder reaction.

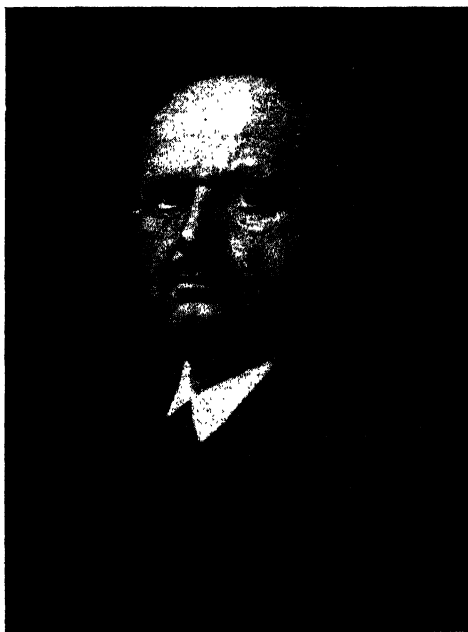
**Diels-Alder Reaction.** In essence this reaction occurs between a conjugated diene and an olefinic carbonyl compound. The olefin adds to the diene in a 1,4-addition and this is accompanied by a shift of double bond in the diene (see page 62). A simple case is the addition of butadiene and acrolein.



Other examples are: Addition of butadiene and maleic anhydride,

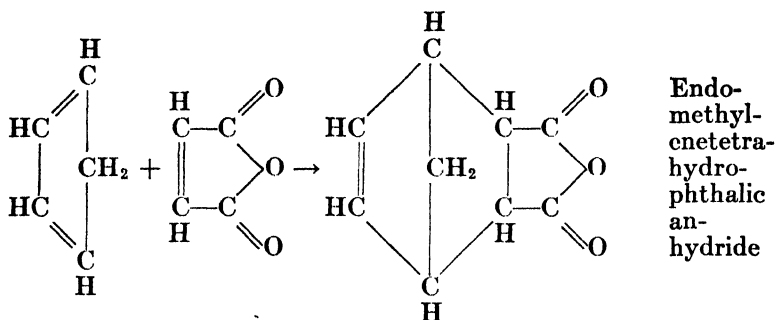


**J. A. NIEUWLAND.** (1878-1936, American.) For many years professor of organic chemistry at Notre Dame University. Nieuwland was a recognized authority in the chemistry of acetylene. His work was basic for the preparation of Neoprene rubber. He is responsible for the development of the use of boron fluoride as a catalyst in organic synthesis. Nieuwland had a strong interest in botany and published nearly one hundred papers in that field. He was founder of the *American Midland Naturalist*, founder of the Nieuwland Herbarium (at Notre Dame). See *Ind. Eng. Chem.*, (News Edition), **14**, 248 (1936); also *Ind. Eng. Chem.*, **27**, 847 (1935).



**HANS FISCHER.** (German, 1881-1945.) Fischer received the Nobel prize in 1930 for work which included the synthesis of hemin. He was head of the Organic-Chemical Institute of Munich Technical High School. See *J. Chem. Education*, **8**, 185 (1931), *ibid.*, **15**, 351 (1938); also this book, page 704.

## Addition of cyclopentadiene and maleic anhydride,



The reactions shown here and the many others of similar type take place readily, often at room temperature. The reaction has very great possibilities. See formation of limonene, page 634.

TABLE 41.—CYCLOALKANES

Name	Formula	M.p., °C.	B.p., °C.	Sp. g., 20°/4°
Cyclopropane.....	(CH <sub>2</sub> ) <sub>3</sub>	-126.6	-34 <sup>749</sup> mm.	0.720 <sup>-79°</sup>
Cyclobutane.....	(CH <sub>2</sub> ) <sub>4</sub>	-50	11-12 <sup>726</sup> mm.	0.703 <sup>0°</sup>
Cyclopentane.....	(CH <sub>2</sub> ) <sub>5</sub>	-93.3	49-50	0.745
Cyclohexane.....	(CH <sub>2</sub> ) <sub>6</sub>	6.5	80-1	0.779
Cycloheptane.....	(CH <sub>2</sub> ) <sub>7</sub>	-12	118-20	0.810
Cyclooctane.....	(CH <sub>2</sub> ) <sub>8</sub>	14.4	150-1 <sup>749</sup> mm.	0.839

## REVIEW QUESTIONS

- Write the graphic formulas for: (a) Cyclobutane; (b) Cyclononane; (c) Methyl cyclohexyl ketone; (d) 1,1-Dichlorocyclobutane; (e) 1,3-Dimethylcyclopentane.
- Show the reaction between isoprene and maleic anhydride; between cyclohexadiene (conjugated) and maleic anhydride.
- Would you expect to make cyclopropanone by heating calcium succinate? Why?
- (R) Which compounds studied in the vitamin and hormone sections might be included in the study of alicyclic compounds?
- Quintol (cyclohexane-1,4-diol) exists in two forms. Explain this by the use of graphic formulas.
- Interpret the tendency of ethylene to add reagents in terms of the strain theory.
- In using the tetrahedron to represent carbon atom in various compounds we have always used a regular tetrahedron. This assumes that any forces which might cause distortion of the model are the same for all of the molecules shown. Is this assumption justified? What bearing has your answer on the proper interpretation of the Baeyer strain theory?
- Draw graphic formulas for the *cis* and *trans* forms of cyclohexane. Do we have such isomerism with cyclopentane? Why?
- Make graphic formulas for the possible isomeric forms of dimethylcyclobutane. How many kinds of isomerism are possible?
- Plot on cross-section paper the boiling points of the cycloalkanes (ordinates) and the number of carbon atoms therein (abscissas). In the same way (and on the same sheet)

plot density versus number of carbon atoms. Plot on the same sheet the boiling points and densities of the saturated open-chain hydrocarbons of like carbon content. Discuss possible reasons for the differences noted between the values of the constants of alkanes and cycloalkanes.

11. Account for the fact that in the synthesis of compounds in which large rings are formed, the yields are quite low.
12. Calculate the percentage composition of carbon and hydrogen for the hydrocarbons  $C_{20}H_{40}$  and  $C_{21}H_{44}$ . Would it be easy to uphold these formulas entirely on the basis of a quantitative analysis? Cite those facts which would be needed to put each compound into its proper class. What additional measurements would be required to substantiate these formulas?

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## CHAPTER XXXIII

### TERPENES

The essential (distillable) oils of certain plants, of trees such as the pine, and of citrus fruits, contain hydrocarbons of the formula  $C_{10}H_{16}$ . These are the true terpenes, a group of substances having close chemical relationships. The distillation of caoutchouc (india rubber), itself a plant product, yields isoprene of formula  $C_5H_8$ , which is termed a *hemiterpene*.

Other terpenes found in nature include: the Sesquiterpenes,  $C_{15}H_{24}$ ; Diterpenes,  $C_{20}H_{32}$ ; and Polyterpenes,  $(C_5H_8)_n$ .

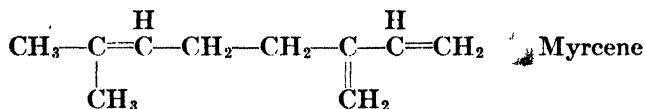
Terpenes are obtained from their natural sources by steam distillation and by extraction with solvents. A few are solids, but the majority are colorless liquids having a boiling point between  $155^\circ$  and  $185^\circ$ . Their odors are characteristic and pleasant. Many are optically active.

Terpenes include both open-chain compounds and cyclic compounds containing one and two rings. Chemically, they are very active substances; their chemistry presents many new features and is far from simple. Addition reactions are common, due to the presence of one or more double bonds in these compounds. Polymerization also occurs in certain cases. A full discussion of terpene chemistry is more pertinent to a technical monograph, and here no more can be attempted than a presentation of the simpler features.

#### OPEN-CHAIN TERPENES

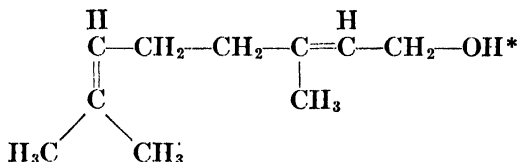
These are olefinic hydrocarbons and their alcohol and aldehyde derivatives, the presence of which in the essential oils of plants and flowers is in large part responsible for their agreeable odors. A certain similarity of structure will be noted in the formulas shown below, and later we shall find that there is a strong resemblance between these structures and those of the cyclic terpenes.

**Myrcene**, which occurs in bay oil, is an example of an open-chain terpene. It is a triolefin whose chain consists of two isoprene units (see page 627).



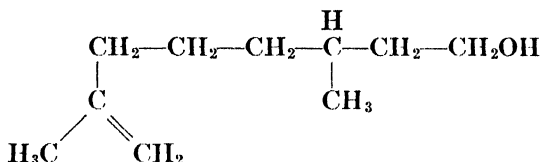
Following are several of the aldehyde and alcohol derivatives of open-chain terpenes.

**Geraniol.** Geraniol is found in oil of rose and geranium, in lavender, citronella, etc.



**Citral,** Geranial, the aldehyde corresponding to geraniol, is found in oil of lemon-grass and of orange, and other essential oils. It is employed in the manufacture of ionone (page 635) and as a flavoring agent.

**Citronellol.**



This is found in rose oils, and geranium oils, and is used in rose perfumes. Its acetate is also used in perfumery.

**Citronellal** is the aldehyde of citronellol, used in perfumery. It is an important constituent of oil of citronella. This oil has been used as a mosquito repellent.

## RUBBER

The product we know as rubber is formed by the coagulation of the juice (latex) of trees or shrubs which are successfully grown in the Far East, in South America, Africa, and to a lesser extent in more temperate climates. The principal source is the tree *Hevea brasiliensis*. The coagulation of the latex may be caused by the use of acetic acid or other acids or salts, or by evaporation. It will also coagulate on standing. It may be preserved by addition of ammonia and in other ways; large amounts of latex were imported as such to be used directly in industry. Such latex is used in making cord tires and a variety of dipped articles (gloves, etc.). It is possible to deposit rubber from the latex by use of the electric current, as the particles in the latex have a negative charge. In this way even deposits may be built up on odd-shaped forms.

For rubber manufacture the coagulated latex is run through mills and washed, later it is ground or masticated in mills; various fillers are added (finely divided carbon black, zinc oxide, barium sulfate, etc.). The incorporation of fillers saves rubber and also improves the quality of the finished

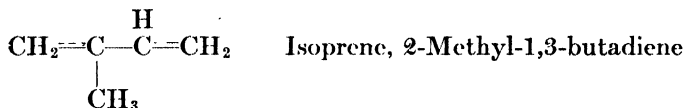
\* Because of the double bonds in the chain, citral and geraniol can occur in *cis* and *trans* forms. The natural citral is a mixture of these and the *cis* and *trans* forms of another isomer, having the left-hand double bond at a different station.

product. "Rubber" fulfills so many purposes in modern life that over 30,000 different formulas are in use by rubber makers, and about 2000 different materials are blended in the various mixtures.

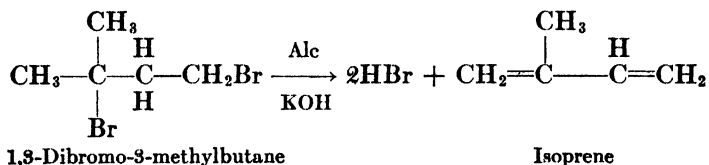
The rubber may now be molded to various shapes by the application of heat and pressure. For most uses it will require vulcanization. Unvulcanized rubber has some undesirable properties; it becomes brittle at low temperatures, it softens in hot weather, it is soluble in organic solvents, it is easily oxidized and hardened by exposure to air.

In vulcanization the rubber is heated with sulfur. Accelerators are added to hasten the reaction between sulfur and the double bonds of the rubber hydrocarbon.\* Rubber so treated loses its sticky consistency and gains greatly in elasticity and stability to temperature changes. Anti-oxidants are added with the accelerators to protect the rubber against aging. In the vulcanization of soft rubber about 5 per cent of sulfur is used. Large amounts of sulfur (20–50%) give hard rubber.

Untreated rubber contains the characteristic substance caoutchouc, a terpene of the formula  $(C_5H_8)_n$ . Its distillation gives principally isoprene,  $C_5H_8$ , polymers of isoprene, and other products.



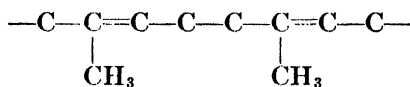
Isoprene has been synthesized in several ways. The following is the method of Ipatieff, by which the hydrocarbon is formed by loss of hydrogen bromide from dibromomethylbutane:



By treatment with acids, alkalis, or with metallic sodium, isoprene has been successfully polymerized to a form of rubber and such synthetic rubber has been vulcanized. It is of interest to note that isoprene may be made in good yield from turpentine by a process of recent discovery. It is possible that isoprene rubber will compete with other synthetic rubbers if this process is sufficiently developed. See also page 62.

\* Well known accelerators are "Captax" (mercaptobenzothiazole),  $C_6H_4N=C(S)\cdot SH$ , "Altax" (dibenzothiazyl disulfide),  $[C_6H_4N=C(S)]_2$ , Tetramethylthiuram disulfide,  $(CH_3)_2NCS SS CSN(CH_3)_2$ . The latter will vulcanize rubber without the addition of any elemental sulfur.

**Structure of Rubber.** Synthetic rubber produced from isoprene is presumed to have a long-chain structure built up from isoprene units by 1-1, 1-4, or 4-4 linkages. Natural rubber also has a long-chain structure, but it is thought to have only the 1-4 type of union between the isoprene units.



Carbon linking in rubber chain (?)

Various molecular weights of rubber have been reported (100,000 to 300,000).

#### ELASTOMERS (SYNTHETIC RUBBER-LIKE PRODUCTS)

Difficulties inherent in the large-scale production of isoprene have led to the use of other compounds of similar structure for polymerization to rubber-like materials. The following table lists the compounds of chief interest.

TABLE 42.—COMMERCIAL ELASTOMERS

Elastomer	Starting compounds	Peak yearly production, 1943-4 (tons)*	Maker
Ameripol.....	1,3-butadiene, copolymerized with other compounds (formulas not disclosed)	.....	B. F. Goodrich Co.
Hycar.....	As for Ameripol	.....	B. F. Goodrich Co.
Chemigum.....	As for Ameripol	.....	Goodyear Tire and Rubber Co.
Butyl rubber.....	Butenes with small amount of diolefins	132,000	Standard Oil Co.
Buna S (Amprene)...	1,3-butadiene and styrene (copolymers)	845,000	Standard Oil Co., Firestone Tire and Rubber Co.
Perbunan.....	1,3-butadiene and acrylonitrile (copolymers)	.....	Standard Oil Co., Firestone Tire and Rubber Co.
Thiokol.....	Ethylene dichloride and sodium polysulfide	60,000	Dow Chemical Co.
Koroseal.....	Vinyl chloride with plasticizers (tricresyl phosphate)	.....	B. F. Goodrich Co.
Neoprene.....	Chloroprene (see below)	69,000	E. I. du Pont Co.
Vistanex.....	Isobutylene	.....	Standard Oil Co.
Resistoflex.....	Vinyl alcohol (?)	.....	Resistoflex Corp.

\* These preliminary figures were revised during 1943 as the volume of production of synthetic rubber increased.



Some of the materials listed on page 507 might be included in this list since there is no hard and fast definition of "synthetic rubber."

The majority of the elastomers are prepared as an emulsion in water. The mixture resembles latex and may be similarly used for the impregnation of fabrics. The solid elastomers are coagulated by the use of a weak acid as in the case of natural latex. Due to the varying composition of the elastomers there are corresponding differences in the methods of vulcanization. Koroseal may not be vulcanized.

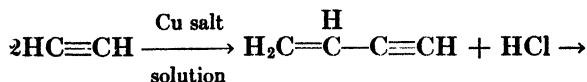
The synthetic elastomers are in general superior to natural rubber in resistance to abrasion and to the action of oils and organic solvents; also in resistance to sunlight.



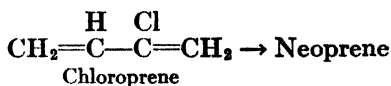
FIG. 101.—Vessels for polymerization of synthetic rubber. (Courtesy of The B. F. Goodrich Company.)

*Butyl rubber* differs in structure from the polymers made from diolefins. It is made from butenes with a small addition of diolefins and the polymer is unsaturated only to about the extent required for the reaction with sulfur in vulcanization. The finished butyl rubber thus avoids the unsaturation of natural rubber, believed to be responsible for poor aging and for oxidation.

*Synthesis of Neoprene.* The following running equation outlines the steps in the synthesis of neoprene, starting with acetylene.



Vinylacetylene\*



\* Divinylacetylene, which is formed in the same reaction, is polymerized to make S.D.O.

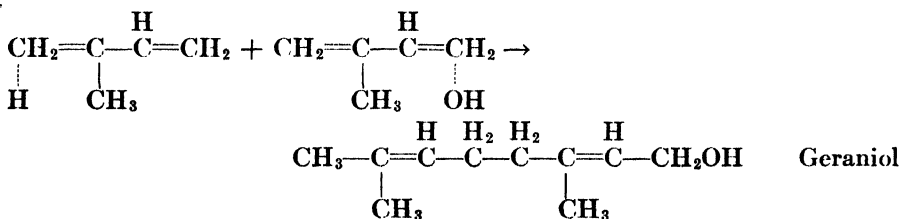
It will be seen that isoprene and chloroprene differ only in the replacement of a methyl group by chlorine atom. The more negative chlorine is probably responsible for the rapid polymerization of chloroprene. Again, the polarity of the molecule caused by the presence of chlorine atom probably leads to a more regular type of union as with natural rubber, rather than the irregularity noted in isoprene rubber.

**Rubber Chloride; Plioform.** An interesting reaction of rubber is that with chlorine. The resulting rubber chloride has about 68% halogen and on this account does not burn. It is used to form paints which are fast to acid and alkali, and is suitable for use in plastics.

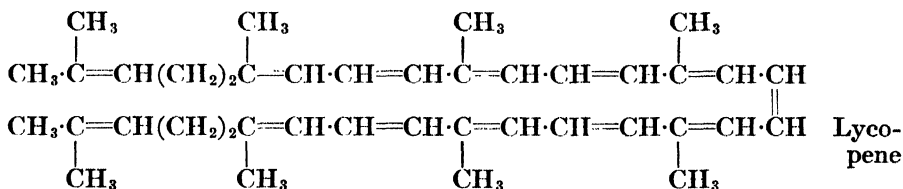
Other reagents which have been applied to rubber are: hydrogen, halogen acids, organic halides, nitrogen compounds, various acids, stannic chloride. Plioform is made by the use of chlorostann (ic) or (ous) acid.

**Plioform**, made by reaction with hydrogen chloride, is employed as a wrapping material.

**Isoprene as a Building Block.** The isoprene unit is a very important natural building block. It occurs, for example, in vitamin A, in vegetable and flower pigments, and in the simple terpenes as well. The relationship of isoprene to geraniol (two isoprenes plus water), shown herewith, is a good example.



**Lycopene** is the red coloring matter of the tomato. Its formula shows the recurring isoprene unit. See also Carotene, page 748.

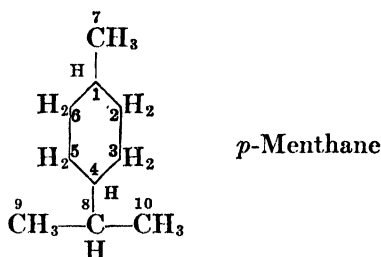


### MONOCYCLIC TERPENES

Monocyclic terpenes are derivatives of *para* and *meta* cymene (methyl-isopropylbenzene). However, since these terpenes all have two double bonds, it is more convenient to consider them as derived from the corre-

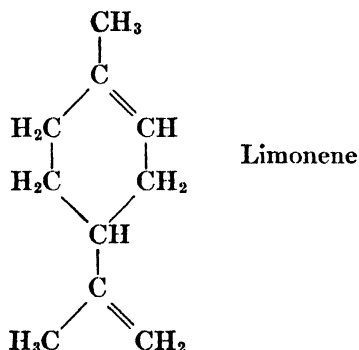
(Synthetic Drying Oil) for incorporation into paints. It gives a quick-drying, hard, water-resisting finish. The "drying" effect is caused by further polymerization, which occurs after the solvent evaporates.

sponding completely reduced hexahydrocymenes, which are called menthanes. The monocyclic terpenes, then, are *p*- or *m*-menthadienes.



The possibilities for isomerism in the terpenes are very numerous; *p*-menthadiene, for instance, has fourteen isomers. The number of possible isomers is still further increased by the presence of asymmetric carbon atoms in these compounds, thus allowing for stereoisomerism. The presence of the double bonds gives the terpenes an olefinic character which is retained when one or both double bonds lie within the ring. (We have already noted that dihydrobenzene and tetrahydrobenzene are olefinic in character; page 409.)

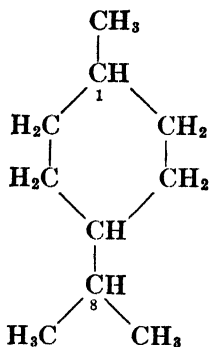
**Limonene.** One of the most common of the monocyclic terpenes is limonene, which occurs in its *d*, *l*, and racemic forms in oil of lemons, orange blossom oil, oils of bergamot, caraway. The distillation of caoutchouc also yields limonenes along with isoprene, etc. Racemic limonene, known as dipentene, is one of the products obtained by heating isoprene to 300°C. (see page 634). Its structure is as follows:



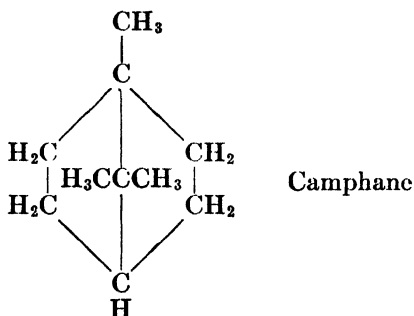
Other monocyclic terpenes are the terpinenes, phellandrenes, carvestrene, sylvestrene, which are menthadienes derived from *p*- and *m*-cymene.

#### DICYCLIC TERPENES

Like the monocyclic terpenes, the dicyclic compounds are derived from cymene. The second ring is formed by the inclusion of the isopropyl group within the benzene ring, as will be more easily understood by reference to the following graphs:

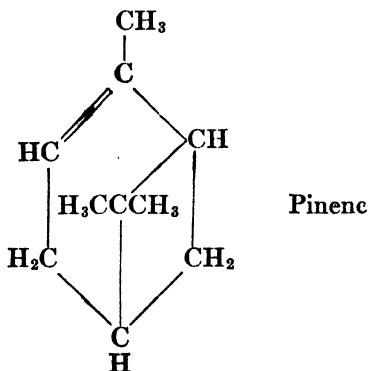


If we imagine the isopropyl group of *p*-menthane to have been taken within the benzene ring, joining carbon 8 to carbon 1, the resulting structure is that of a dicyclic compound (Camphane), similar in structure to certain dicyclic terpenes.



Other compounds of this group have the "bridge" joining *meta*\* and *ortho*† carbon atoms, as well as a *para* junction as shown here.

**Pinene.** The most widely distributed compound of this group is pinene, which occurs in turpentine, pine-needle oil, and other sources, in both *d* and *l* forms.

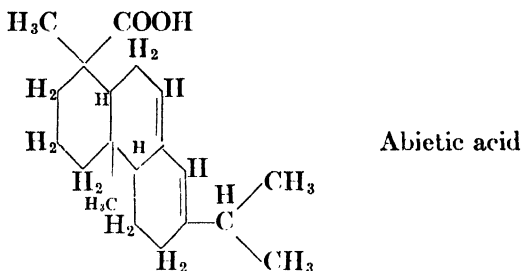


\* Pinane group.

† Carane group.

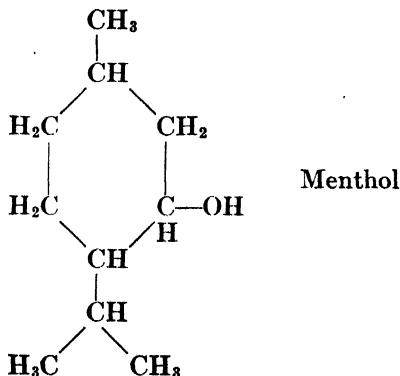
The "hydrochloride" of pinene has an odor like camphor and is called artificial camphor. The use of turpentine as a solvent in paints and varnishes is familiar to all. It is also a good solvent for rubber, iodine, sulfur. Rosin or colophony is the resin which remains as a residue when crude turpentine is distilled. It is used in resin soaps, in sealing wax, shoe wax, lubricants, as well as for sizing paper, as a paint drier, and a starting compound in synthesis of other resinous materials.

An important acid of rosin is abietic acid, used as a varnish drier and in synthetic work.



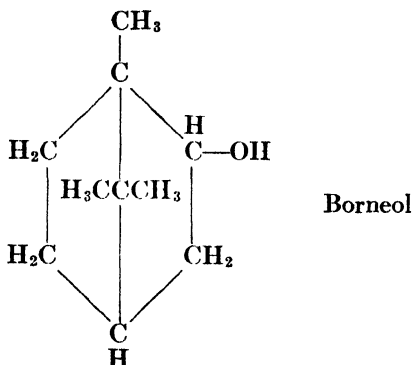
#### IMPORTANT TERPENE DERIVATIVES

**Menthol.** This is an alcohol of the menthane series, found in peppermint oil. It is used as an analgesic and antiseptic, for toothache, asthma, and in perfumery; also in face creams and ointments, on account of the cooling sensation it imparts to the skin.



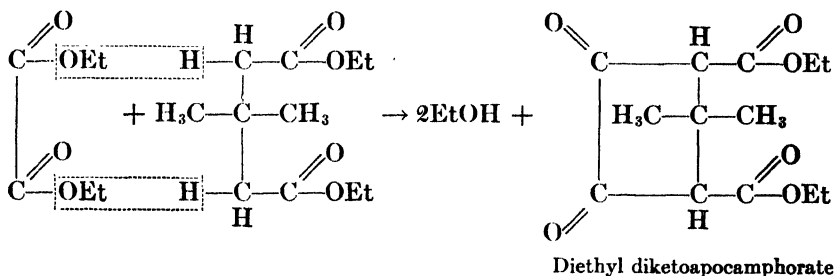
**Thymol** is the cymene derivative corresponding to menthol. It is discussed on page 508. A derivative of thymol, dithymol diiodide, known as aristol, is a well known antiseptic and iodoform substitute.

**Borneol** is an alcohol, found as the acetate in oils of thyme and valerian. Its oxidation yields camphor. It is used in perfumery, as is the acetate.



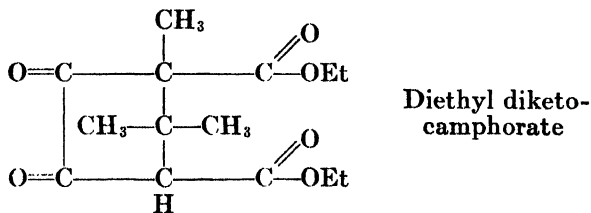
**Camphor** is a ketone terpene derivative. It is obtained from the camphor tree of Formosa, Japan, and China. It is a white friable solid of characteristic odor, which is taken from its natural source by steam distillation, or the application of boiling water. Its insecticidal powers have led to its use in "moth balls," for which purpose it has been replaced to some extent by other compounds (page 584). Camphor is used somewhat in medicine as a sedative, analgesic, circulatory stimulant. It is largely employed in the preparation of celluloid and pyralin, also for making smokeless powder.

**Syntheses of Camphor.** The importance of camphor has stimulated chemical research leading finally to its artificial preparation. The Komppa and Haller synthesis of camphor begins with the condensation of diethyl oxalate with diethyl  $\beta,\beta$ -dimethylglutarate:

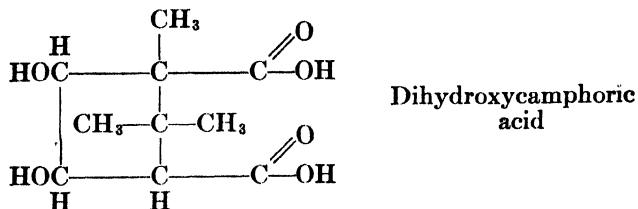


The various steps from this point comprise:

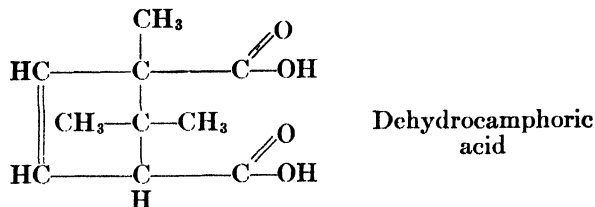
(1) Introduction of methyl group by the use of sodium and methyl iodide:



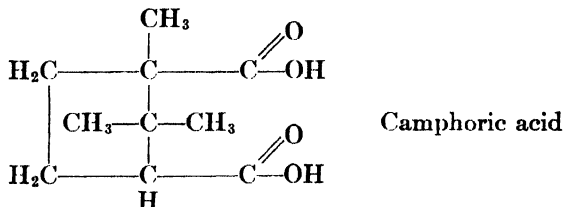
- (2) Reduction and hydrolysis to dihydroxycamphoric acid:



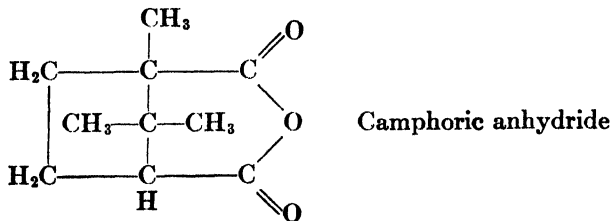
- (3) Conversion to dehydrocamphoric acid by treatment with hydriodic acid and red phosphorus:



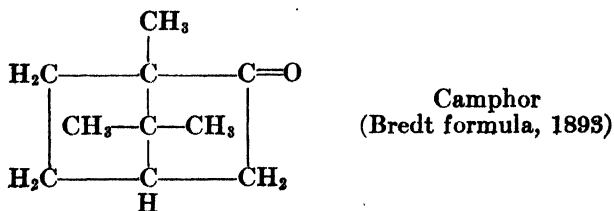
- (4) Addition of hydrogen bromide, and reduction with zinc and acetic acid, to camphoric acid:



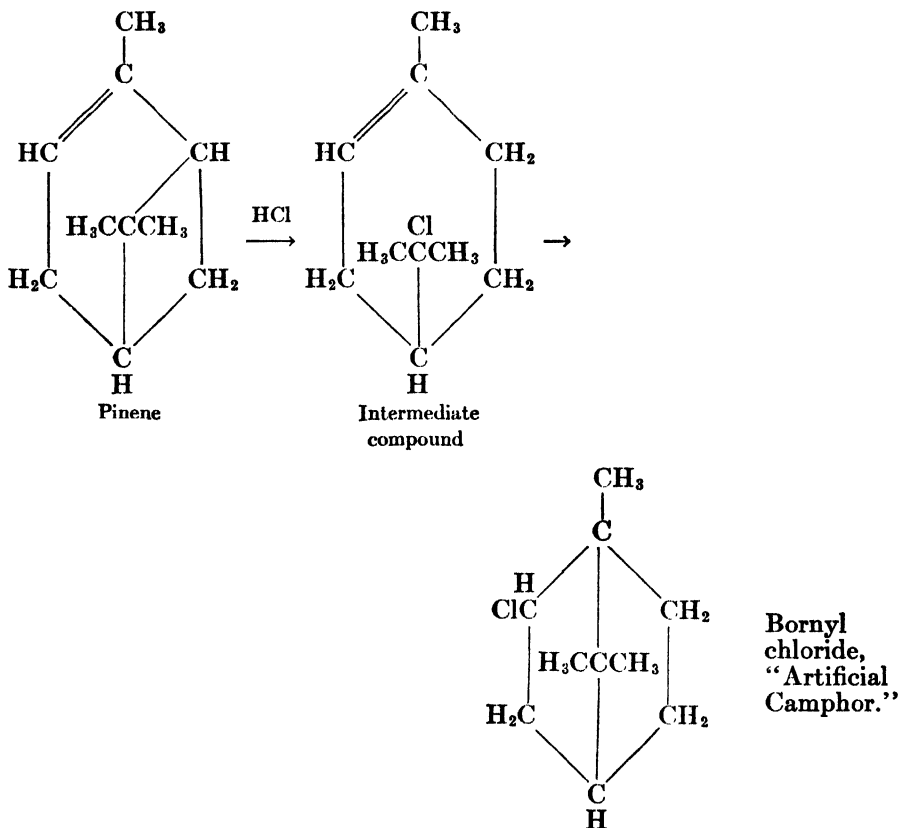
- (5) Camphoric acid is converted to its anhydride:



- (6) The anhydride by several additional reactions yields camphor:



The above synthesis was extremely important as it furnished a proof of the structure of camphor. A simpler method of synthesis involves the treatment of pinene from turpentine with hydrogen chloride:



A rearrangement takes place during this reaction and the final product is bornyl chloride,\* which, after conversion to its acetate, followed by hydrolysis, yields borneol. The oxidation of borneol produces camphor.†

Borneol acetate has the odor of pine-needle oil. It is a useful side-product of this synthesis.

#### RELATIONSHIP OF OPEN-CHAIN AND CYCLIC TERPENES

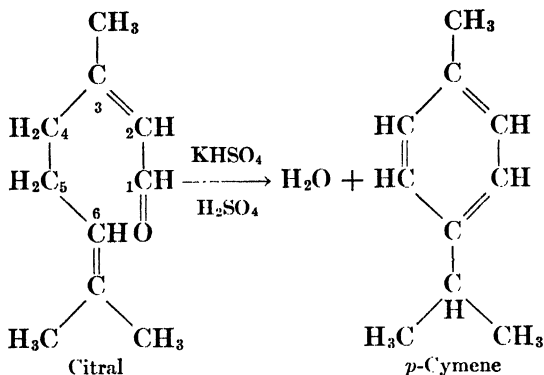
A comparison of the formulas of the cyclic and open-chain terpenes shown in this chapter will reveal a close similarity in structure. This is more noticeable if the formula of the open-chain compound is made into an open ring as shown below for citral. It is quite apparent that if this ring

\* If pinene is heated with oxalic, benzoic, or other organic acid, the corresponding ester of borneol is produced.

† See RITTER. A new camphor synthesis. *J. Am. Chem. Soc.*, **55**, 3322 (1933).

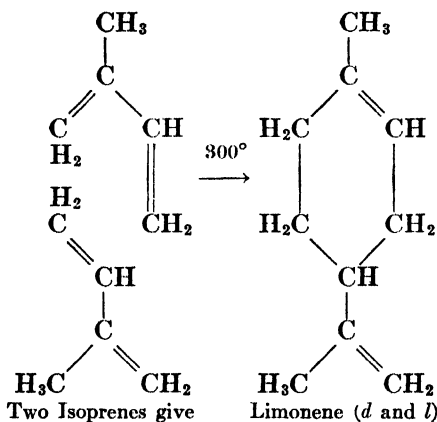


were closed by joining carbons 1 and 6, the resulting structure would represent a derivative of *p*-menthane. This transformation can, in fact, be carried out. Citral, when treated with potassium bisulfate and dilute sulfuric acid, is converted by loss of water to cymene:



Other examples of this type of change have made it clear that the relationship between open-chain and ring terpenes is more than purely formal. The transformation of ring terpenes to open-chain compounds has also been effected, though not by such simple means as illustrated here.

#### Relationship of Isoprene to Ring Terpenes.

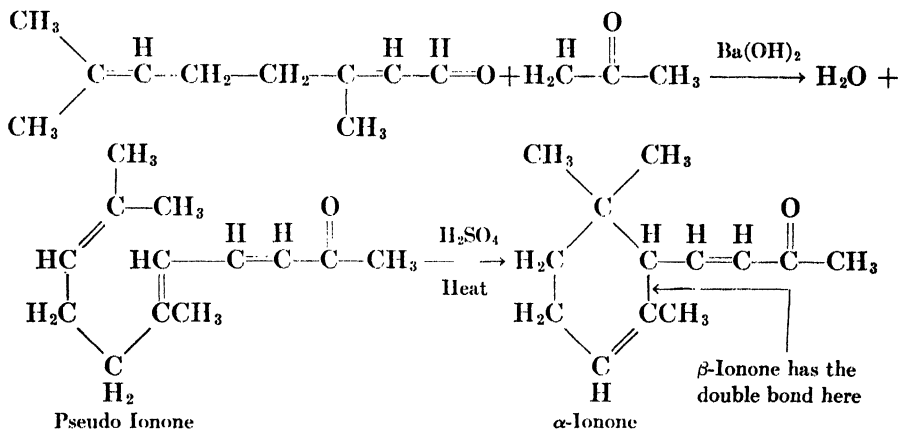


The scheme above shows how a derivative of *p*-menthane can be formed from isoprene. Similar schemes could be shown for the formation of the *meta* compounds. Whether or not these syntheses actually take place in nature, the relationship is suggestive and interesting.

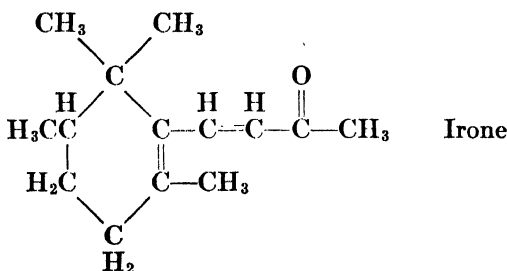
If the synthesis occurs, its order very probably is: (1) union of two isoprene molecules to form an open-chain terpene; (2) cyclization to a ring terpene.

## SYNTHETIC PERFUMES, FLAVORS

**Ionone.** The substance irone, found in violets and responsible for their fragrance, has been closely imitated both in structure and properties by the ionones, condensation products of citral and acetone.



A proposed formula for irone is given below for comparison with the formulas of the ionones.



Syntheses such as this, by which complex molecules are cleverly built up from inexpensive originals, are highly prized by organic chemists.

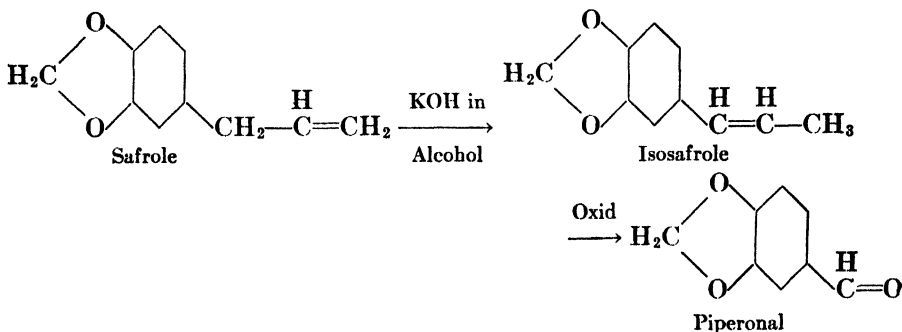
While considering the subject of perfumes and flavors, certain substances may be brought in which find such employment, though not related to the terpenes in a chemical sense. Some of these compounds are found in nature in the same source as the terpenes, and in fruits. A few have already been discussed on previous pages.

### *Esters.*

Amyl acetate.....	Used in pear essence.
Ethyl acetate.....	Used in essence of pear, cherry.
Amyl butyrate.....	Used in apricot essence, in pineapple oil.
Methyl salicylate.....	Used in oil of wintergreen.
Amyl valerate.....	Used in apple essence.

*Aldehydes, ketones.*

Benzophenone.....	page 557
Cinnamic aldehyde.....	In oil of cinnamon.
Vanillin.....	Vanilla flavor, made from eugenol, the chief constituent of oil of cloves (see page 553).
Benzaldehyde.....	Bitter almond oil.
Piperonal.....	A product of synthesis, also occurs in the heliotrope. It can be made from safrole, the chief component of sassafras oil, by a series of reactions like those used to form vanillin from eugenol.



In this case, as in the example on page 553, a double bond shifts so as to form a conjugated system with other double bonds.

*Ethers.*

Eugenol.....	In oil of cloves.
Anisaldehyde.....	Anise flavor.
Diphenyl ether.....	page 498.
$\beta$ -Naphthol methyl ether.....	page 589.

*Other Compounds.*

Coumarin.....	page 653.
$\beta$ -Phenylethyl alcohol.....	page 493.
Cinnamyl alcohol.....	page 493.
Benzyl benzoate.....	page 493.
Methyl anthranilate.....	page 526.
Methyl salicylate.....	page 529.
Phenylacetic acid.....	page 531.
Musks.....	page 446.

In considering the competition of synthetic perfumes with natural compounds, the following data are of interest:

For one ounce of natural violet oil about twenty-five tons of flowers are needed.

A ton of roses yields about ten ounces of oil.

Lilac and lily of the valley perfumes have not been obtained successfully from flowers. The marketed products are synthetic.

The use of terpenes in perfumes has more than an esthetic side, for as has been stated, a number have considerable antiseptic value. Citral, eugenol, thymol, menthol, safrole, and citronellol, all rank much higher than phenol in antiseptic power. Many have distinct medical uses, and all told, these compounds hold a prominent position in organic chemistry.

TABLE 43.—SALES DATA, U.S.A., 1936 AND 1940\*

	Pounds, 1936	Pounds, 1940
Amyl acetate.....	11,776,930	
Amyl salicylate.....	40,898	66,907
Benzyl alcohol.....	148,642	121,084
Coumarin.....	137,506	245,688
Diethyl phthalate.....	856,328	1,869,683
Dimethyl phthalate.....	123,569	
Ethyl acetate.....	55,778,905	60,632,757
Ethyl benzoate.....	1,852	1,635
Isoamyl butyrate.....		6,469
Methyl salicylate.....	1,650,542	1,486,791
Phenylethyl alcohol.....	122,573	171,668
Vanillin.....	293,501	619,407

\* From U.S. Tariff Commission Report.

### REVIEW QUESTIONS

1. Give a working definition of the term "terpene."
2. Define the terms: sesquiterpene, hemiterpene, dicyclic terpene.
3. Discuss the isomerism of citral. Is this isomerism also shown by citronellal?
4. Write the graphic formula of vitamin A and indicate by the use of dotted lines the position of isoprene units in the molecule. Do the same with the formula of limonene.
5. Show by equations the probable course of the reaction between bromine (bromine-water) and geraniol. Would a dilute solution of potassium permanganate be affected by geraniol?
6. What tests could be used to distinguish geraniol from citral?
7. Show by means of graphic formulas and discussion the relations which exist between borneol, camphor, and menthane.
8. Give steps in the synthesis of camphor from pinene.
9. Write equations for the reaction between borneol and benzoic acid.
10. Show by graphic formulas and discussion the relationship between the open-chain and the monocyclic terpenes.
11. List five substances of three different chemical classes which are used as perfumes or flavors. Show by equations the synthesis of each compound.
12. Discuss the sources of the terpenes and the means employed in their isolation.
13. Why should a perfume be a fairly good antiseptic?
14. Does limonene have any double bonds? How should it react with an excess of bromine?
15. Explain how it is possible for limonene to exist in *d* and *l* forms. Does it have any asymmetric carbon atoms? Answer this same question for pinene.
16. What compound should be formed by the complete reduction of menthol? of borneol? What is the relationship of the two reduction products?

17. Give a list of reagents which could be used to detect the carbonyl group of camphor.
18. Write equations for four chemical reactions of dihydroxycamphoric acid
19. Discuss, with specific details, the medical uses of terpenes.
20. Discuss the industrial uses of terpenes
21. What physical and chemical properties are of assistance in the identification of a terpene?

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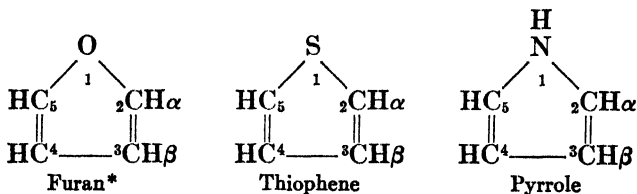
## HETEROCYCLIC COMPOUNDS

Ring compounds having rings composed solely of carbon atoms are called homocyclic compounds, or carbocyclic compounds. When other atoms are incorporated in the ring we have heterocyclic compounds. Among the atoms, other than carbon, used in ring formation are nitrogen, oxygen, and sulfur; less familiar compounds have phosphorus, selenium, etc., as ring-forming elements. Substances like cyclic anhydrides (succinic anhydride), lactones, etc., may be classed as heterocyclic, but are not generally considered apart from the open-chain compounds from which they are derived, because they easily revert to these compounds by hydrolysis or other simple reactions. The rings we are to consider are much more stable.

The reactions of all the single-ring heterocyclic compounds have some points of resemblance with benzene chemistry; however this analogy is sometimes very slight. For this reason a thorough consideration of these substances is not a part of an elementary study of organic chemistry. The number of known heterocyclic compounds is very large. The majority are derived from five- and six-atom heterocyclic nuclei, or from condensed nuclei.

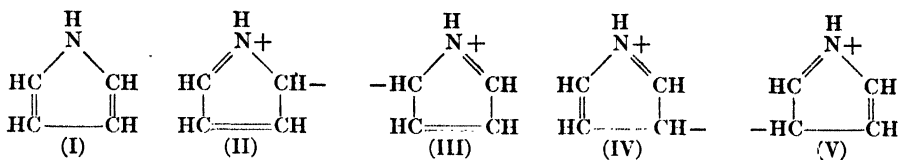
## FIVE-ATOM HETEROCYCLIC NUCLEI

Five-atom nuclei built up of carbon and the atoms oxygen, sulfur, and nitrogen are Furan, Thiophene, and Pyrrole.



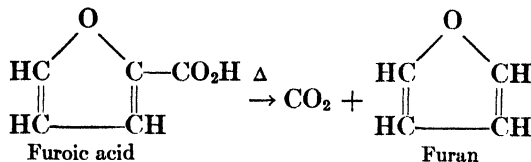
A similarity of structure will be noted in these formulas; each has a system of double bonds and a hetero atom which can form "onium" compounds. The three functions are conjugated with each other as in benzene. Thus we may expect these compounds to show "aromatic" properties. The stability of the compounds is increased by resonance (see page 398); for example, pyrrole resonates between the forms (I), (II), (III), (IV), and (V).

\* The formulas in this chapter show the hetero atoms of single ring compounds at the top, which is the latest approved way of writing them. In the journal literature and in other books they will frequently be found reversed, or perhaps turned to the side. Some of the condensed heterocyclic compounds are written with the hetero atom at the bottom.

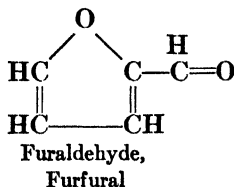


The resonance energy of furan, thiophene, and pyrrole is 23, 31, and 31 Kg. cal. per mole respectively.

**Furan**, which is a colorless low-boiling liquid, is obtained when pyromucic (furoic) acid is heated to its boiling point:



Its most interesting derivative is *furaldehyde* (furfural). This is a liquid having a peculiar empyreumatic odor. It is like benzaldehyde in its reactions, i.e., it yields a phenylhydrazone, undergoes the Cannizzaro reaction (page 491), and yields furoin by methods which with benzaldehyde produce benzoin.



Furfural is produced from pentoses by distillation with sulfuric or hydrochloric acid. A small amount is easily obtained in this way from bran. Corn cobs, straw, and other plant substances also yield furfural on similar treatment. Furfural is volatile in steam, and in experiments like the above it is detected by holding a paper moistened with aniline acetate solution in the escaping vapor. The furfural forms with this reagent a scarlet-colored derivative.

Furfural is today produced in very large quantities by the digestion of oat hulls with steam under pressure, in presence of dilute sulfuric acid. It can be applied to the manufacture of synthetic resins of the type of Bakelite. It is used as a solvent for cellulose esters, and in paint removers. Further uses include: resin solvent, especially for abrasive wheels, preparation of shoe dyes, special solvent for purifying lubricating oils (see page 41), as a fungicide, weed killer. Derivatives of furan which have been prepared and studied include furfuryl alcohol, furfuramide, furoin, furil, substituted furoic acids, furoic esters, etc.

**Thiophene**,  $C_4H_4S$ , occurs in commercial benzene in a concentration of about one-half per cent. It may be removed by repeated shakings with

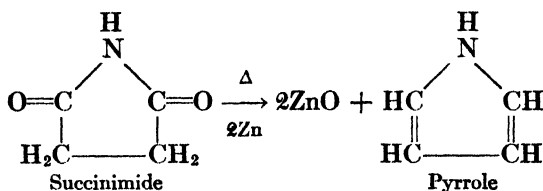


concentrated sulfuric acid, or by warming with the same reagent. Thiophenesulfonic acid, soluble in water, is formed, while the benzene is practically unaffected. Thiophene may be prepared from its sulfonic acid, but more conveniently from sodium succinate and phosphorus trisulfide.

Thiophene, with a small amount of isatin dissolved in sulfuric acid, gives an intensely blue-green solution. At one time this was presumed to be a test for benzene. Victor Meyer however made the discovery (1882) that pure benzene, made from benzoic acid, did not give the test. The discovery of thiophene and many derivatives is due to his researches following this accidental occurrence. The continued presence of thiophene in commercial benzene is explained by its boiling point ( $84^{\circ}$ ), which is close to that of benzene. Many derivatives of thiophene have very nearly the same boiling points as the corresponding benzene derivatives, e.g.,

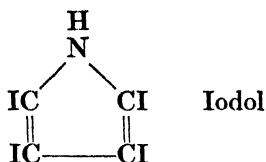
	B.p.		B.p.
Nitrobenzene.....	$210.9^{\circ}$	2-Nitrothiophene.....	$225^{\circ}$
Toluene.....	110.8	2-Methylthiophene.....	112-3
Chlorobenzene.....	132.1	2-Chlorothiophene.....	130
<i>p</i> -Dichlorobenzene.....	173	2,5-Dichlorothiophene.....	170

**Pyrrole**,  $C_4H_5N$ , was originally discovered in bone oil (Dippel's oil), a product of the dry distillation of bones, from which it may be isolated by combined chemical and physical means. It may be synthesized by the reduction of succinimide, brought about by distillation with zinc dust:



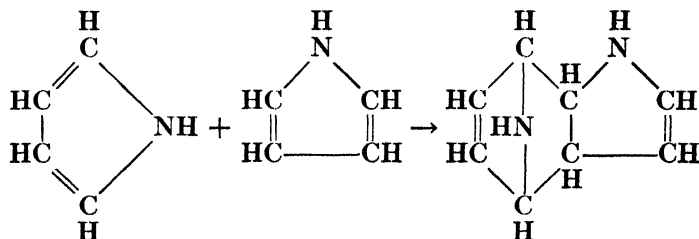
Small amounts of pyrrole are found in coal tar. It is a colorless liquid, with an odor like that of chloroform, but slightly water-soluble, soluble in ether and alcohol.

Chemically, pyrrole is a weak base due to the  $=\text{NH}$  group, also it may act as an acid, the imide hydrogen being replaceable by potassium. However the salt so formed is completely hydrolyzed by water. With the halogens pyrrole forms substitution derivatives as does benzene, but with greater facility. Tetraiodopyrrole:



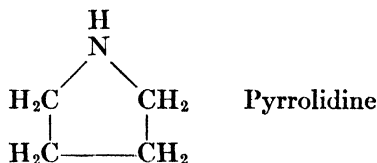
also known as Iodol, is an antiseptic. Its action is like that of iodoform, but it is odorless, non-irritant and insoluble in water.

Pyrrole polymerizes quite readily, especially when treated with acids. Thus hydrochloric acid gives a trimer. This may possibly be formed by a Diels-Alder reaction between molecules. The formation of a dimer by this reaction is shown in the following equation.

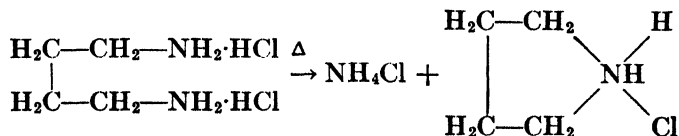


The vapor of pyrrole forms a red compound in contact with a pine shaving moist with hydrochloric acid. The reaction may be used as a test for small amounts of pyrrole; certain derivatives of pyrrole also give this test. We note the pyrrole or pyrrolidine ring in many natural products, for example in nicotine, cocaine, atropine, chlorophyll, hemoglobin.

**Pyrrolidine.** By complete reduction pyrrole is converted to pyrrolidine:



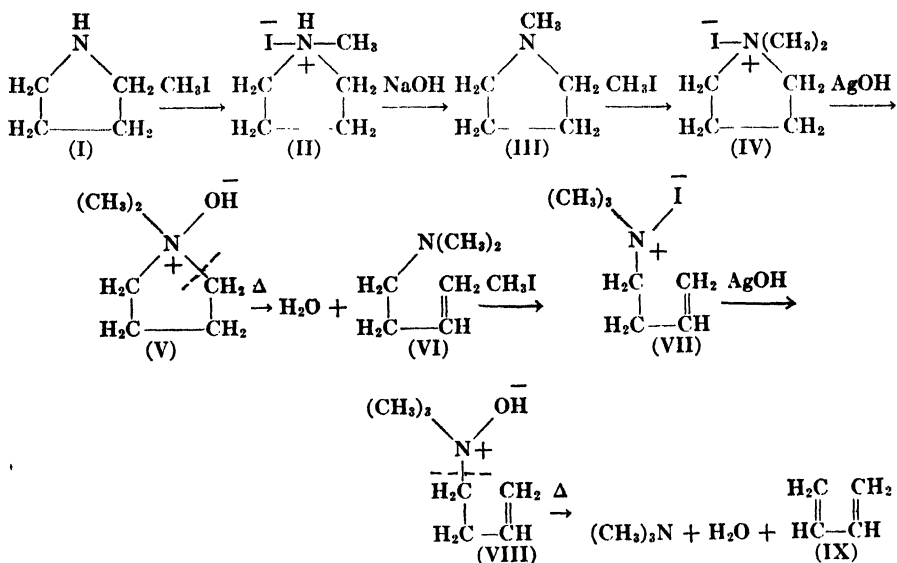
The compound may also be formed by heating tetramethylenediamine dihydrochloride and treating the resulting salt with a base:



Pyrrolidine is a strongly basic liquid having an odor like pepper. Its *alpha* carboxylic acid, proline, also hydroxyproline, are decomposition products of the proteins (page 719).

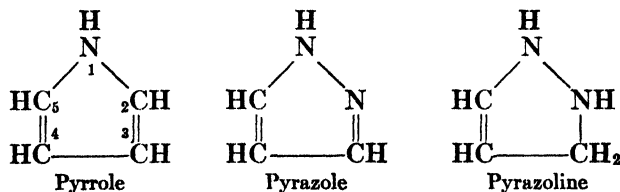
Treatment of pyrrolidine with  $\text{PCl}_5$  opens the ring to give 1,4-dichlorobutane. This synthesis is valuable.

**Exhaustive Methylation.** On page 312 it was shown that a tetraalkylammonium base when heated will undergo a decomposition which separates the nitrogen atom from the largest alkyl group. The method may be used with certain *saturated* nitrogen ring compounds; in this application the ring is broken and the nitrogen atom is removed from the compound. The method, known as exhaustive methylation, is of assistance in determination of the structures of complex nitrogen heterocyclic compounds such as the alkaloids. It will be illustrated with pyrrolidine.

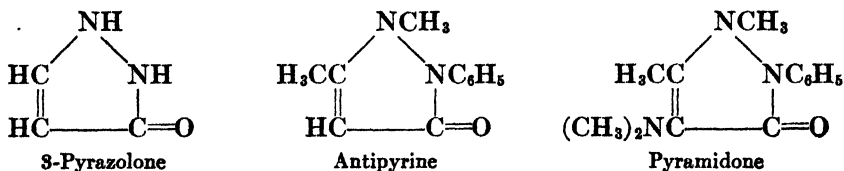


As seen, the method consists in loading the nitrogen atom with methyl groups, then heating the methylated ammonium base (V). The ring is broken and water is formed, one of the ring hydrogens being abstracted in the process. Repetition of these reactions removes the nitrogen atom from the compound leaving a diolefin. The structure of the original compound is deduced from that of the diolefin.

The compound pyrazole is closely related to pyrrole, having an additional nitrogen in the ring. Its reduction product is known as pyrazoline. See below:



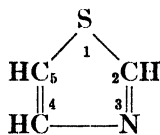
**Pyrazolone**, the ketone derived from pyrazoline, has several important derivatives used in medicine. These are antipyrine and pyrimidone:



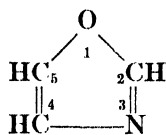
Pyrimidone is useful in the treatment of fever, headache, influenza.

Five-atom heterocyclic compounds are known with three and four nitrogen atoms in the ring, also compounds having oxygen and nitrogen, or

sulfur and nitrogen. Examples of the last mentioned type are thiazole and oxazole.

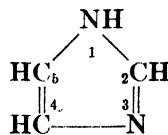


Thiazole



Oxazole

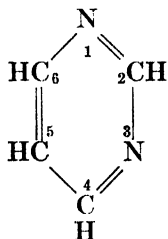
(Known in derivatives  
only)



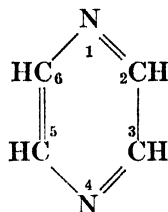
Imidazole

Note that vitamin B<sub>1</sub> (page 749) contains the thiazole ring. See also sulfathiazole (page 647).

Six-atom rings with two hetero atoms are represented by pyrimidine and pyrazine:



Pyrimidine  
(See Vitamin B<sub>1</sub>,  
page 749)



Pyrazine  
(See Vitamin B<sub>2</sub>,  
page 749)

### SIX-ATOM HETEROCYCLIC COMPOUNDS

But one member of this class will be discussed. This is pyridine, C<sub>5</sub>H<sub>5</sub>N. Pyridine is found in coal tar, in bone oil, also in tobacco smoke and in crude ammonia. It may be synthesized by the oxidation of piperidine. It is a colorless liquid with a nauseating odor, soluble both in water and in organic reagents. Its water solution is faintly alkaline to litmus. On account of its disagreeable properties, pyridine is used to denature alcohol. It is an excellent solvent for organic compounds, also for many salts. The alkaline powers of pyridine are put to use when it is employed in reactions to remove and bind halogen acid, for example in the Schotten-Baumann reaction.

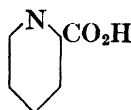


Pyridine (Formula of Körner, 1869)

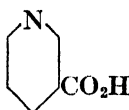
Pyridine is the simplest of the compounds about which the alkaloids are built (see next chapter). It may be looked upon as benzene in which —C= has been replaced by —N=. The arrangement of bonds is like

that in benzene. Like benzene, pyridine is a resonating molecule; the resonance energy is about 40 Kg. cal. per mole. Pyridine is even more stable toward oxidizing agents than is benzene, though it may more easily be reduced. As pyridine dissolves potassium permanganate and is not affected by it, the solution may be used for oxidation of other compounds.

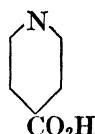
Substitution by halogen atom, nitro, or sulfo groups is more difficult than with benzene. Alkyl side-chains on the pyridine ring oxidize to carboxyl, as with benzene. The following acids result:



Picolinic acid



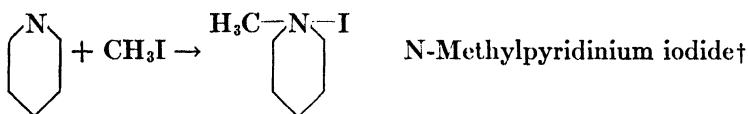
Nicotinic acid\*



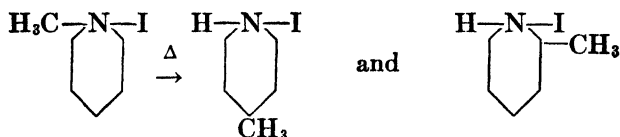
Isonicotinic acid

Like the phthalic acids of the benzene series, these pyridine acids are used as "reference compounds," to determine the relative position of groups on the ring (page 418). The positions on the pyridine ring are indicated by letters or by a number system (see formula).

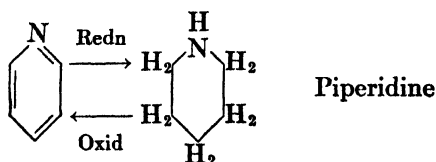
Pyridine reacts with acids to form stable salts, and adds alkyl halides, producing pyridinium derivatives:



When a pyridinium salt is heated a migration of the alkyl group takes place, just as happens with substituted amines of the benzene series (page 460).



Complete reduction of pyridine yields piperidine:



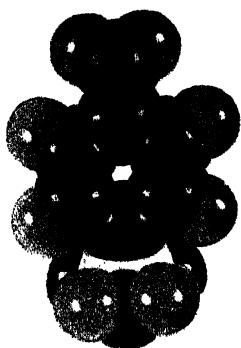
The latter may be synthesized by heating pentamethylenediamine hydrochloride, which loses ammonium chloride. Piperidine is a liquid whose odor

\* Nicotinic acid is being used with success in the treatment of pellagra, which is stated to be a deficiency disease caused by lack of the acid and its amide. See page 750.

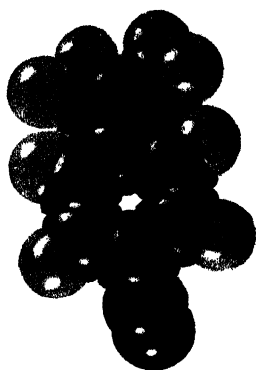
† See footnote, page 447.



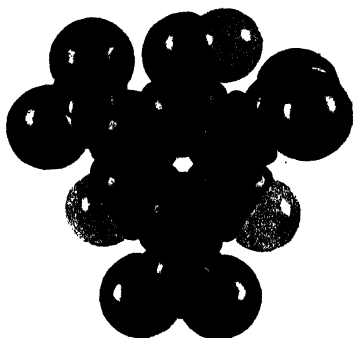
Acetanilide



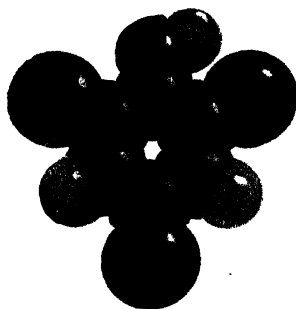
Sulfanilamide



p-Nitrosodimethylaniline



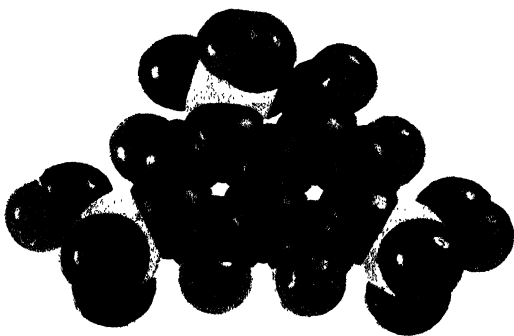
Picric acid



2,4,6-Trichlorophenol



Phenacyl chloride

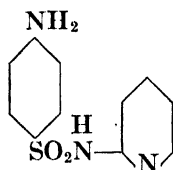


1-Naphthylamine-2,6,8-trisulfonic acid

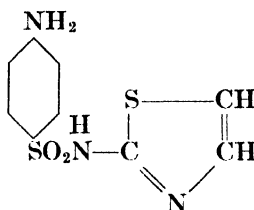


resembles that of ammonia. It may be obtained from the alkaloid piperine, a constituent of pepper (page 660).

It has been mentioned that the pyridine nucleus is found in important alkaloids. It is also present in vitamin B<sub>6</sub> (page 750), and in nicotinic acid (page 750). Two "sulfa" drugs based on pyridine and thiazole respectively are sulfapyridine and sulfathiazole. Both are important in medicine (see page 470) in treatment of pneumonia, gonorrhea, other infectious diseases.



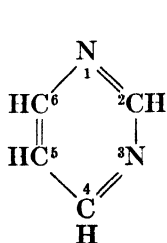
Sulfapyridine



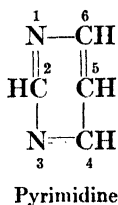
Sulfathiazole

### PYRIMIDINE DERIVATIVES

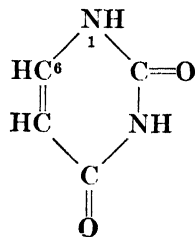
The pyrimidine bases are decomposition products of the nucleoproteins. Two types of formulas are shown for these compounds; one type is that proper to heterocyclic compounds, the other, the rectangular type, is still in use with many chemists.



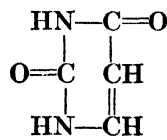
or



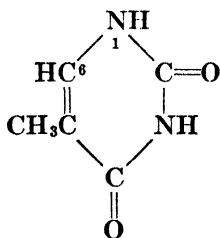
Pyrimidine



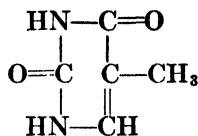
or



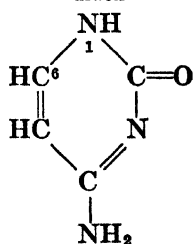
Uracil, 2,4-Dioxy-pyrimidine



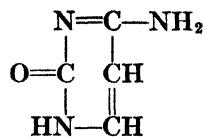
or



Thymine, 5-Methyl-uracil



or

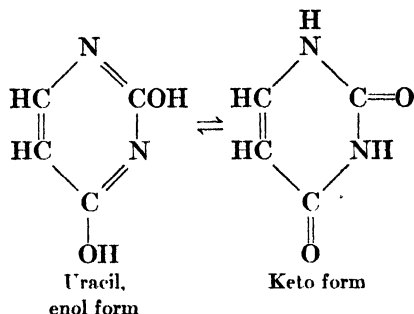


Cytosine, 2-Oxy-6-amino-pyrimidine



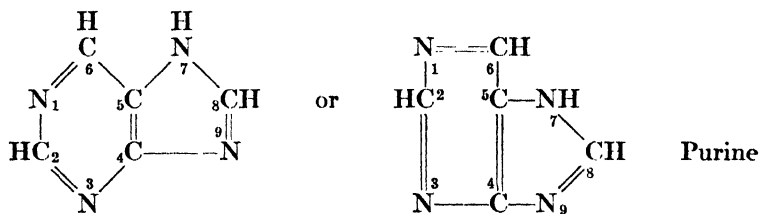
Inspection of these formulas shows that the pyrimidine ring is contained in the structure of uric acid, page 278, and in that of purine, below. The oxygen derivatives of pyrimidine, like those of purine, show keto-enol tautomerism.

Example:

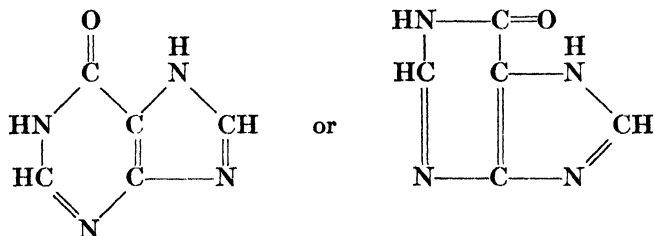


#### PURINE DERIVATIVES

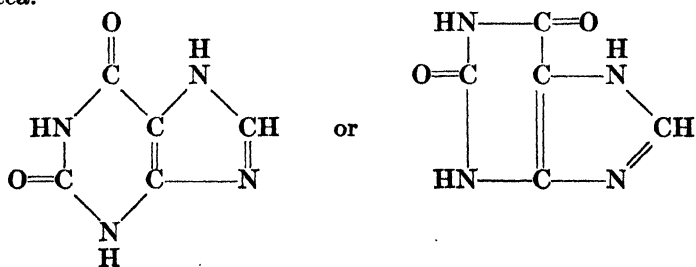
Important natural compounds are built upon the purine nucleus.



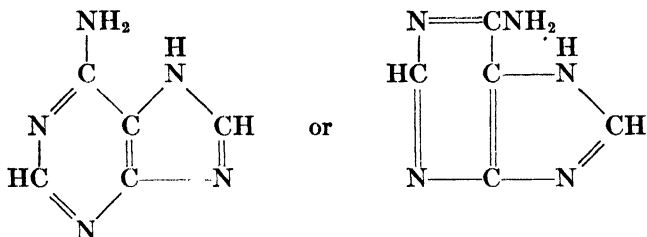
**Hypoxanthine, 6-oxypurine.** Present in blood, urine, etc.



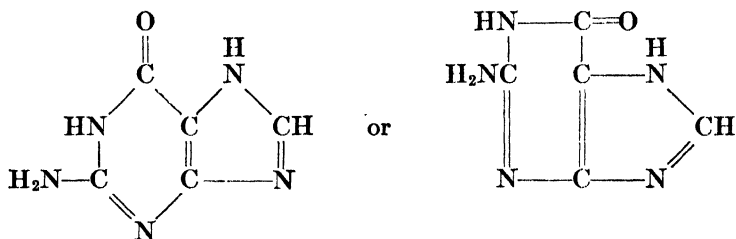
**Xanthine, 2,6-dioxypurine.** This is found in the liver, blood, urine, also in tea.



**Adenine, 6-aminopurine.** Found in extracts of animal tissue.

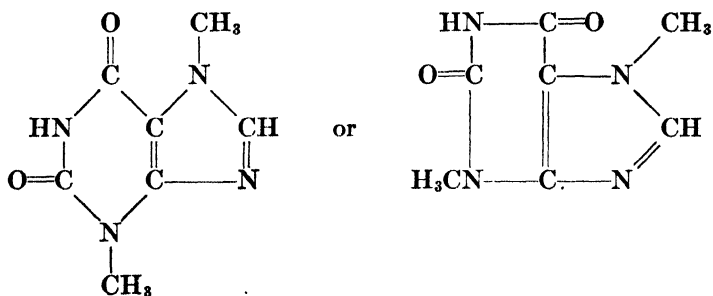


**Guanine, 2-amino-6-oxypurine.** Present in the liver, pancreas, also in animal tissues, and in guano.

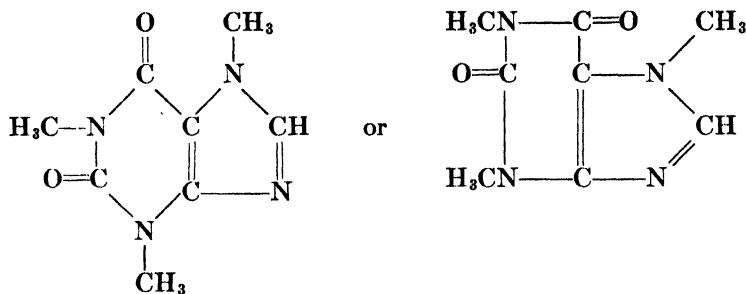


These purine bases are products of the decomposition of the proteins of cell nuclei (nucleoproteins), as are the pyrimidine bases.

**Theobromine, 3,7-dimethylxanthine.** This is present in cocoa beans to the extent of 1 or 2%. It is a diuretic and a stimulant.



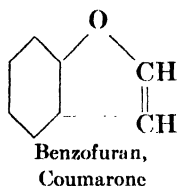
**Caffeine, 1,3,7-trimethylxanthine.** Caffeine is found in coffee beans ( $\frac{1}{2}\%$ ) and in tea (2-4%). It acts as a diuretic, also as a stimulant to the heart and central nervous system. It relieves fatigue and quickens the brain, but habitual excess in its use is harmful to the digestion.



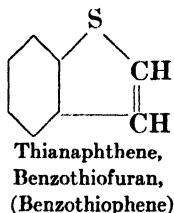
**Theophylline** which is 1,3-dimethylxanthine, and isomeric with theobromine, is found in tea leaves. It is used as a respiratory stimulant.

#### OTHER CONDENSED HETEROCYCLIC COMPOUNDS

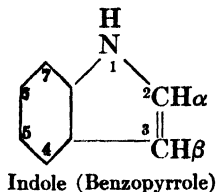
Several condensed heterocyclic compounds of interest are formed by fusion of the benzene ring with the five-membered rings already discussed in this chapter. Examples of such compounds include the following:



**Benzofuran** occurs in coal tar. Treatment with acid gives coumarone resins.

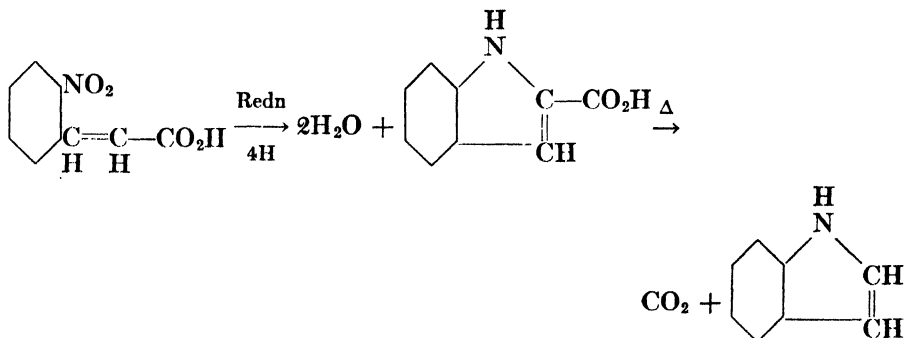


**Thianaphthene** occurs in lignite coal tar. Its odor is like that of naphthalene.



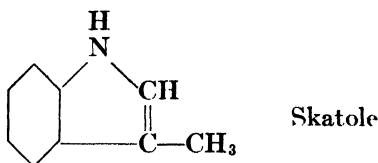
**Indole** is formed in the body upon the decomposition of certain proteins and will be discussed later in that connection (page 761). It is also important through its relationship to indigo (page 693).

Indole is found in nature in coal tar, also in oils of jasmine, neroli, clove flower. It is used in perfumery. One method of synthesis is by reduction of *o*-nitrocinnamic acid:



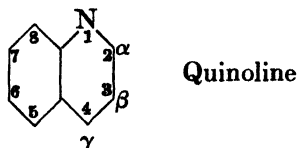
**Indole-3-acetic acid** has been found in plants. It is a growth hormone or auxin, now being marketed for forcing growth of roots on plant cuttings. Indolebutyric acid (Hormodin), and Naphthalene-1-acetic acid are similarly used. See Reference 13, page 657.

**Skatole**, or 3-methylindole, is present in the feces. It is formed when certain proteins putrefy. Its odor is intensely disagreeable.



By the fusion of a benzene and a pyridine ring two important compounds are formed, quinoline and isoquinoline. It will be noted in the following chapter that both of these compounds serve as nuclei of alkaloids.

**Quinoline.** This is a colorless liquid with a pleasant characteristic odor. It is present both in coal tar and in bone oil,\* but is commonly obtained synthetically by the Skraup method. It is insoluble in water.

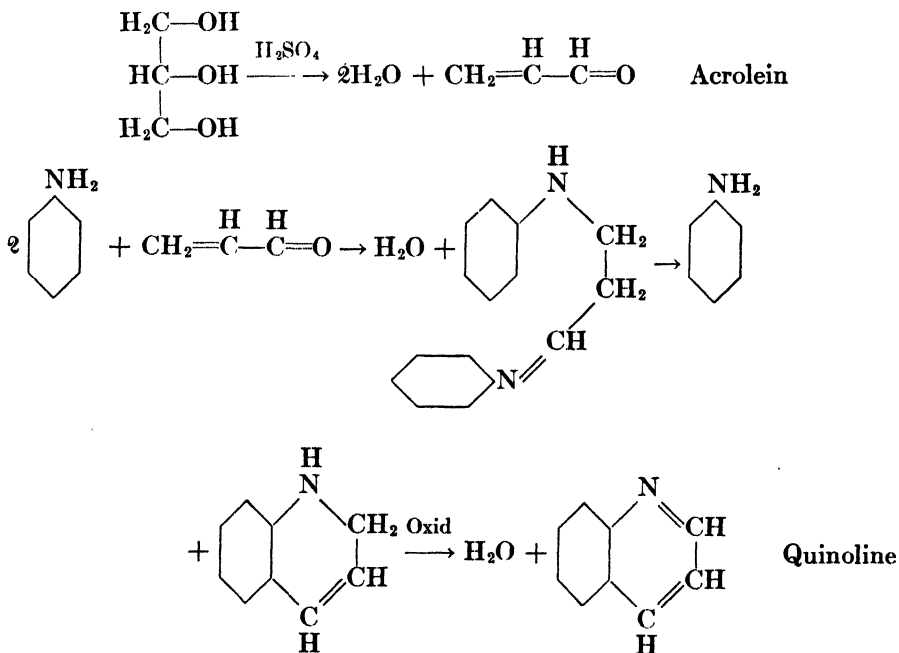


Quinoline bears the same relationship to pyridine that naphthalene does to benzene. It resembles pyridine in its chemistry. Thus it combines with methyl iodide by addition, and it is alkaline to litmus. The differences in

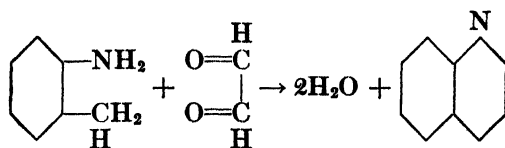
\* Alkylated quinolines and isoquinolines and other nitrogen bases are present in petroleum in small amounts, and may possibly have commercial significance, for example in the preparation of insecticides.

reactivity between pyridine and benzene are clearly seen in this compound where both rings are together. Substitution affects the benzene ring exclusively, and groups are brought into the pyridine ring by indirect methods. Oxidation attacks the benzene ring first, while reduction first affects the pyridine ring. The structural relationship of quinoline and naphthalene has been pointed out; however, it should be noted that quinoline shows the greater complexity, of which an instance is seen in the fact that quinoline has seven monosubstitution products, while naphthalene has but two.

Skraup synthesis of quinoline.



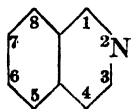
In performing this synthesis, aniline, glycerol, nitrobenzene or arsenic acid (oxidizing agent), and sulfuric acid are mixed in the proper proportions. The above equations illustrate the probable course of the reaction. Another synthesis of quinoline involves the use of glyoxal and *o*-toluidine:



Quinoline has a strong antiseptic action. It and several of its salts are used in medicine. Formulas for quinine and plasmochin, used in the treatment of malaria, are shown on page 661. Both of these are quinoline derivatives.

The compound 8-hydroxyquinoline is of considerable interest in connection with inorganic quantitative analysis. It yields colored precipitates with many metals, which are sufficiently insoluble in water to meet the needs of quantitative analysis. Many other organic compounds are now being used in this way in analytical work, among which may be mentioned dimethylglyoxime, salicylaldehyde,  $\alpha$ -nitroso- $\beta$ -naphthol, aurintricarboxylic acid, and many others. These form complex compounds with the metals as suggested on page 615 in connection with alizarin.

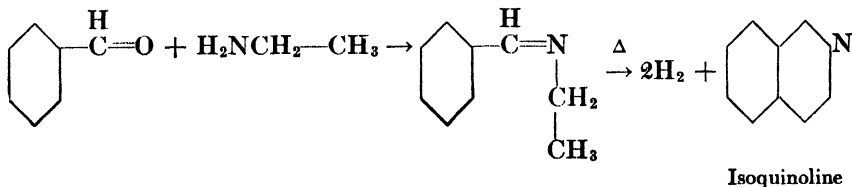
**Isoquinoline.** There are two ways in which a benzene and a pyridine ring can be united; one of these appears in quinoline, the other gives rise to the isomeric compound called isoquinoline.



Isoquinoline

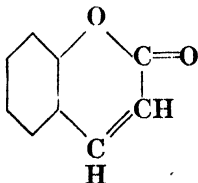
This compound is found in coal tar. It is normally a liquid, with an odor like that of quinoline or benzaldehyde. Isoquinoline is chemically much like quinoline, with the following exceptions: (1) the compound is more basic than quinoline; (2) the pyridine ring is not so stable, and upon oxidation both pyridine and benzene rings are attacked.

Synthesis of isoquinoline from benzaldehyde and ethylamine:



Isoquinoline

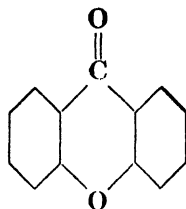
**Coumarin** is a compound of agreeable odor which is present in new-mown hay and tonka beans. It is used as an adulterant for vanillin and for flavoring purposes and perfumes. For synthesis, see page 532.

 $\gamma$ -Pyrone

Coumarin, 1,2-Benzopyrone

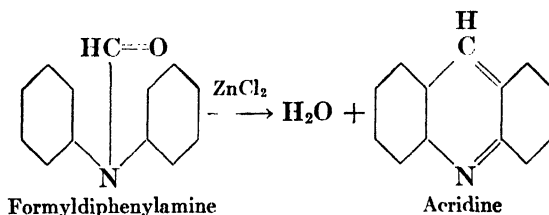
In the following compounds two benzene rings are fused with a five- or six-membered heterocyclic ring.

**Xanthone.** In xanthone we find the heterocyclic ring common to the pyrones. It will be seen that coumarin is a derivative of *alpha* pyrone. We note this ring in several important dyes.



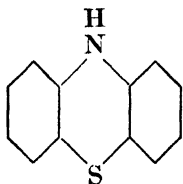
Xanthone

**Acridine** or dibenzopyridine, which occurs in coal tar, may be synthesized from formyldiphenylamine by loss of water:



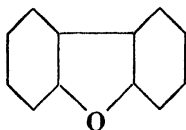
It is the nucleus of the acridine dyes and of several important medicaments. Formulas for acriflavine and proflavine are given on page 700; that of atabrine, a valuable drug for malaria treatment, is shown on page 662.

**Phenothiazine**, whose structure is like that of acridine, is made from diphenylamine and sulfur. It is used as an insecticide and for combating intestinal worms in sheep.



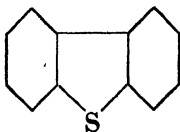
Phenothiazine

**Dibenzofuran** (biphenylene oxide) may be made from phenol by heating with PbO.



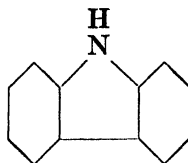
Dibenzofuran

**Dibenzothiophene** (biphenylene sulfide) is formed at high temperature from phenyl sulfide.



Dibenzothiophene

Carbazole or dibenzopyrrole is used in making dyes. It occurs in coal tar.



Carbazole

TABLE 44.—PHYSICAL CONSTANTS OF HETEROCYCLIC COMPOUNDS

Name	M.p., °C.	B.p., °C.	K <sub>A</sub> or K <sub>B</sub>
Furan.....		31.4	
Furaldehyde.....	— 38.7	160.5 <sup>742</sup>	
Thiophene.....	— 30	84	
Pyrrole.....		131	
Pyrrolidine.....		88.5	
Furoic acid.....	132.5	230	$7.1 \times 10^{-6}$
Pyrazole.....	70	186-8	
Pyrazoline.....		144	
Pyrazolone.....	165	Sub., dec.	
Thiazole.....		116.8	$3.3 \times 10^{-12}$
Imidazole.....	89-90	255-6	
Pyridine.....	— 42	115-6	$2.3 \times 10^{-9}$
Picoline (α).....	— 70	128.8	
Picoline (β).....		143.5	
Picoline (γ).....		143.1	
Nicotinic acid.....	232	Sub.	
Picolinic acid.....	137-9	Dec.	
Isonicotinic acid.....	317	Dec.	
Piperidine.....	— 9	106	$1.6 \times 10^{-3}$
Coumarone.....	<— 18	173-4	
Thianaphthene.....	31-2	220-1	
Indole.....	52	253-4	
Skatole.....	95	265-6 <sup>755</sup>	
Quinoline.....	— 15	237.1 <sup>747</sup>	$1 \times 10^{-9}$
Isoquinoline.....	24.6	240.5 <sup>763</sup>	
Coumarin.....	70	290-1	
Xanthone.....	173-4	349-50 <sup>730</sup>	
Acridine.....	110-1	346	
Dibenzofuran.....	86-7	287-8	
Dibenzothiophene.....	97	333	
Carbazole.....	244.8	354.8	

Besides the heterocyclic compounds shown in this chapter others are known whose structures will be found in the larger texts of organic chemistry.

### REVIEW QUESTIONS

- Write equations for the reactions of furaldehyde with the following: (a) KOH solution; (b) Phenylhydrazine; (c) KCN solution; (d) An oxidizing agent.



2. What explanation may be offered for the predominance of five- and six-atom ring structures among cyclic natural compounds?
3. Show by equations the synthesis of pyrrole from ethylene dibromide.
4. How could the above synthesis be modified so as to produce pyrrolidine?
5. Write the graphic formula for 2-nitrothiophene. What should be formed upon its reduction? What benzene compound might have physical properties similar to those of the reduction product?
6. How many isomeric monochlorobenzenes exist? How many monochlorothiophenes? Which of these is listed on page 642? Answer the same questions for the dichloro products.
7. Write equations for the synthesis of a dye compound from furaldehyde, dimethylaniline, etc. (see page 552).
8. Write graphic formulas for: (a)  $\alpha$ -Bromofuran; (b) 2-Iodothiophene; (c) 2,5-Dinitropyrrole; (d) 5-Chloro-2-furoic acid; (e) Pyrrolidine hydrochloride; (f) Oxazole; (g) Pyrazoline; (h) 2,5-Dinitropyridine; (i) Coumarone; (j) 3-Ethylindole; (k) 3,7-Dichloroquinoline.
9. How many isomeric dichloroquinolines should exist? How many dichloroisoquinolines? How many chlorobromoquinolines?
10. Name heterocycles present in the formulas of the following: (a) Coumarin; (b) Anabasin; (c) Quinine; (d) Tropine.
11. Summarize by means of equations the chemical behavior of pyridine.
12. Give equations for the synthesis of pyridine, of quinoline, and of acridine.
13. Write equations for the reactions of quinoline with: (a) Ethyl iodide; (b) A reducing agent.
14. List fifteen compounds of the aromatic series which occur in coal tar. Group these according to their structures and chemistry.
15. Write a complete synthesis of coumarin, beginning with benzene.
16. Which should be the stronger base, pyridine or piperidine? Why?
- (R)17. Do you think that pyrimidine is a colored compound? Why? If it is colored, is it a dye? Why?
18. The formula for acridine is sometimes written with a "para bond." What justification is there for this formulation?
19. Illustrate how a tripolymer may be formed from pyrrole by a Diels-Alder reaction.
20. Show two ways of going from 1,4-diaminobutane to 1,4-dihydroxybutane.
21. Propose a method of synthesis of carbazole based upon those methods given for the synthesis of dibenzofuran and dibenzothiophene.
22. What evidence have we that quinoline has a benzene ring? How do we know that it has a pyridine ring?
23. Give the complete chemical names of antipyrine and pyrimidine.
- (R)24. Write graphic formulas for the tautomeric forms of oxindole and dioxindole.
25. List all compounds described in this chapter which have medical applications, and give specific uses for each compound.

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## CHAPTER XXXV

### ALKALOIDS

The vegetable alkaloids are naturally-occurring, cyclic, nitrogenous, basic compounds. They are found in plants (generally of the class of dicotyledons), combined with organic acids such as lactic, citric, malic, oxalic, etc., commonly found in plants, or with special acids, e.g., meconic acid with morphine, quinic acid with quinine. In some cases they exist as glycosides.

Alkaloids contain carbon, hydrogen, nitrogen, and usually oxygen. They are for the most part colorless solids, though a few which are oxygen free are liquid (nicotine, coniine) and several have a slight yellow color. They are insoluble in water,\* but more or less soluble in organic solvents, and, as most of them are tertiary amines, they unite with acids to form water-soluble salts. These salts, hydrochloride, sulfate, etc., are generally used in medical work.

Alkaloids are optically active (mostly levorotatory), are bitter in taste, and have marked physiological activity, some acting as violent poisons. They are very extensively used in the field of medicine, where they perform most valuable service.

Certain substances known as "alkaloidal reagents" precipitate alkaloids from their solutions; these include tannic acid, picric acid, phosphotungstic acid, and others. The same substances may be used to precipitate proteins. Certain reagents develop strong colors when applied to alkaloids, aiding in their identification. These color tests are taken up in the chapter on "Analysis and Identification."

Study of the alkaloids has shown that they are built up around several well known heterocyclic compounds; these are pyrrole, pyridine, quinoline, and isoquinoline.† These compounds were taken up in the chapter on heterocyclic compounds. In the present chapter alkaloids belonging to each group will be shown, but their reactions and synthesis cannot be discussed in any detail, as the subject is too difficult for elementary treatment.

\* The liquid alkaloids are water-soluble.

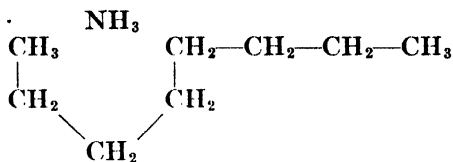
† Caffeine, theobromine, xanthine, and other derivatives of purine, also aliphatic nitrogen bases such as neurine, muscarine, putrescine, cadaverine, choline, ephedrine, epinephrine, etc., several of which have strong physiological action, may be considered as alkaloids. On account of their relationship to non-alkaloidal compounds, however, they are usually termed vegetable bases, while the term alkaloid is reserved for derivatives of heterocyclic nuclei.

## PYRIDINE ALKALOIDS

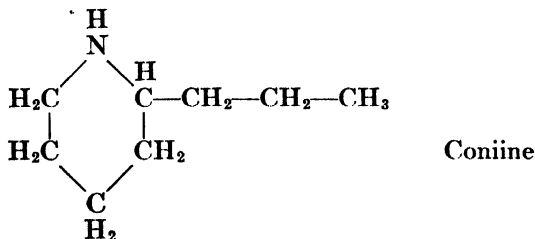
**Coniine.** Coniine is a dextrorotatory liquid alkaloid, obtained from hemlock seeds. It was the first alkaloid to be artificially prepared, and is among the simplest whose structure is known. Coniine is quite poisonous (eight times as toxic as piperidine), about 0.2 gram being a fatal dose. It was with this substance (hemlock juice) that Socrates was put to death. The structure of coniine is determined from its reactions and its decomposition products.

**Structure.** Coniine,  $C_8H_{17}N$ , distilled with zinc dust, yields three molecules of hydrogen and a new compound  $C_8H_{11}N$ , called conyryne. Oxidation of conyryne yields picolinic acid; therefore coniine itself has but one side-chain and this must be in the  $\alpha$ -position (see page 646). The side-chain is composed of three carbons (conyryne,  $C_8$  minus pyridine,  $C_5$ ). Therefore conyryne is either  $\alpha$ -propyl- or  $\alpha$ -isopropylpyridine, and coniine is the corresponding derivative of piperidine.

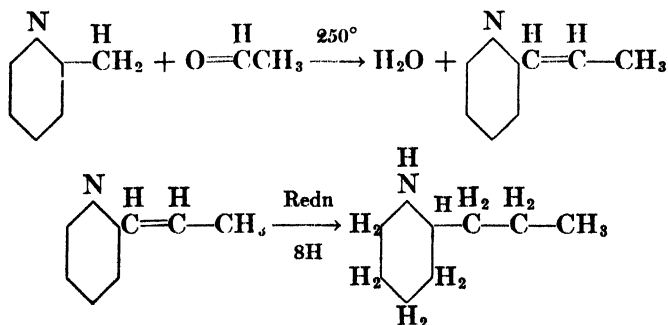
Since the reduction of coniine yields normal octane and ammonia:



the side-chain must be unbranched. Coniine is therefore  $\alpha$ -propyl-piperidine:

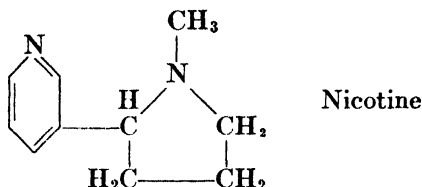


Synthesis of Coniine from  $\alpha$ -picoline ( $\alpha$ -methylpyridine) and acetaldehyde (1886, Ladenburg):



The *dextro* compound, identical with natural coniine, is obtained by fractional crystallization of the tartrates of racemic coniine, the product of the synthesis shown above.

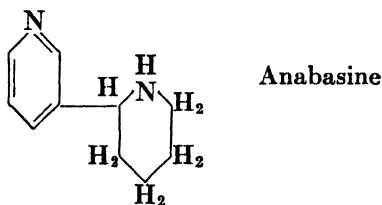
**Nicotine.** Nicotine, obtained from the tobacco plant, is a liquid alkaloid. It is water-soluble, and has a strong odor like that of a foul tobacco-pipe. It is highly toxic, much more so than coniine. Oxidation with nitric acid yields nicotinic acid; therefore it is a pyridine derivative with substitution in the  $\beta$ -position (see page 646). The complete formula is shown below:



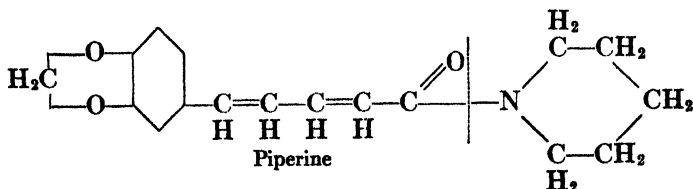
Inspection of this formula shows that nicotine could as well be considered as a derivative of a reduced pyrrole ring (pyrrolidine). By some authors it is so considered, being grouped with atropine and other alkaloids which have this ring.

Nicotine is used as an insecticide and for delousing poultry. Powdered tobacco has been used in the same way. Nicotine thiocyanate has been tried as an agricultural insecticide with good results.

Nicotine has been synthesized. The resulting racemic compound was separated and the *levo* isomer was shown to be identical with nicotine from natural sources. It is more toxic than the *d*-compound. The isomeric compound, *anabasine*, is also used as an insecticide.

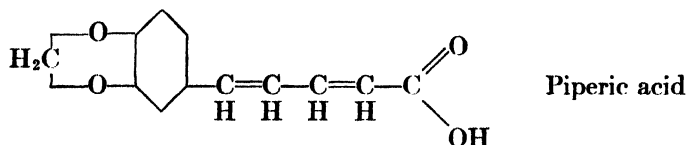


✓ **Piperine.** Piperine is obtained from black pepper, and is a solid, tasteless substance, without optical activity.

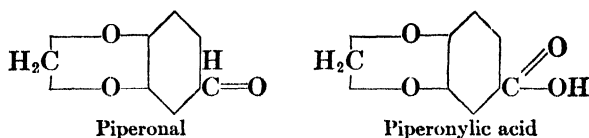


It will be noted that the compound is an amide. Its hydrolysis yields

piperidine and piperic acid, the break occurring at the bond marked with the dotted line.



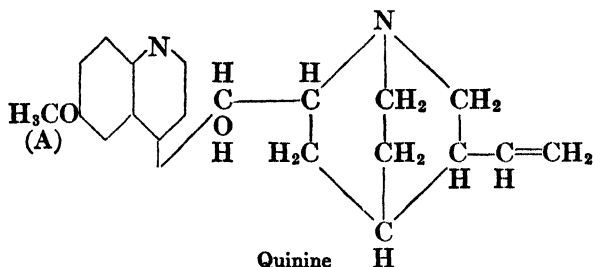
It is interesting to note that the oxidation of this acid, by breaking the double bond near the ring, produces piperonal, a perfume material (page 636) whose name is based upon this method of preparation. Further oxidation yields piperonylic acid:



Piperine is used as an antipyretic and to relieve colic.

#### QUINOLINE ALKALOIDS

**Quinine** and **Cinchonine** are alkaloids found in cinchona bark where they occur with about twenty others.

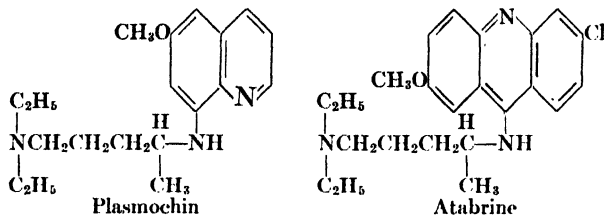


Cinchonine is like quinine in structure but lacks the methoxy group at (A).

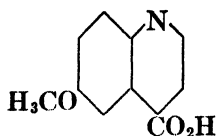
Chief interest attaches to quinine, which has long been used to allay fever and in the treatment of malaria. In malaria it appears to have a specific action as a poison to the parasites, while sparing the cells of the host. Cinchonine has about the same physiological effects as quinine. Quinine and its derivatives have antiseptic and local anesthetic action.

The organisms which cause malaria reproduce in man by simple division but in their other host, the mosquito, sexual forms of the parasite appear. Quinine attacks the asexual form of the parasite (thus relieving malaria), but does not suppress the sexual forms which spread the

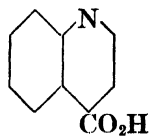
disease. Atabrine, a synthetic antimalarial, acts in a similar way. Plasmochin, another synthetic compound, has an advantage over quinine in that it attacks the sexual forms of the malaria parasite, so preventing spread of the disease. It is used with quinine in treatment of malaria.



Although quinine and cinchonine were first isolated in 1820, their formulas were not fixed until 1931. Their oxidation produces the following acids:



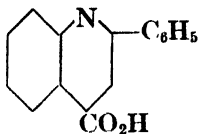
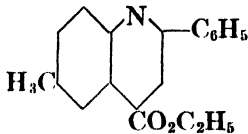
Quininic acid



Cinchoninic acid

whose structures are known. It will be seen that these two acids bear the same relation to their parent alkaloids, and in each case the residue  $C_{10}H_{15}N(OH)$  has still to be accounted for. The structure of this part of the molecule was recently established by synthesis.

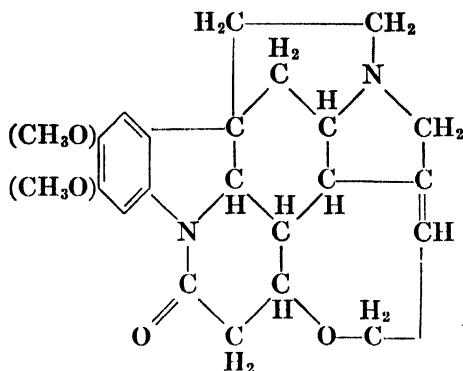
Several derivatives of cinchoninic acid employed in medicine are atophan, 2-phenylquinoline-4-carboxylic acid, and novatophan:

Atophan,  
CincophenNovatophan,  
Neocincophen

Atophan and novatophan are used in treatment of gout. The action is like that of salicylates. Novatophan is less irritating than atophan.

### INDOLE ALKALOIDS

**Strychnine** and **Brucine** are obtained from the seeds of *nux vomica* and from *Ignatius* beans. Strychnine was first isolated in 1818, and its molecular formula was established twenty years later. The skeleton formula given below is not, however, known to be correct, as this alkaloid has not so far been synthesized.



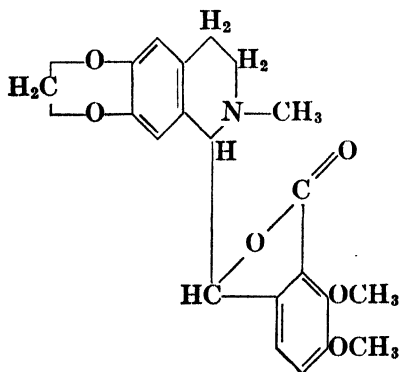
Strychnine,  $C_{21}H_{22}O_2N_2$ , proposed skeleton structure.  
 Brucine,  $C_{23}H_{26}O_4N_2$  is dimethoxystrychnine.

Strychnine is employed in medicine for tonic or stimulating action. Overdoses cause convulsions which resemble those of tetanus. A secondary use for strychnine is for poisoning rats and other animals.

Brucine has a physiological action like that of strychnine, but is less toxic. This alkaloid is frequently used for the separation of optically active substances, according to the method developed by Pasteur (page 339). The more costly alkaloids (Cinchonine, Morphine, etc.) are also used for this purpose when necessary.

#### ISOQUINOLINE ALKALOIDS

From the many alkaloids of this group but one, **Hydrastine**, will be shown. This alkaloid is obtained from the root of golden seal.



Hydrastine

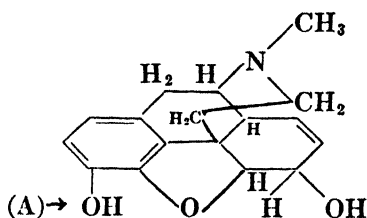
Hydrastine is an astringent and styptic, used to check uterine hemorrhage, etc. Hydrastinine, an oxidation product of hydrastine, is used to check internal hemorrhage.

#### OPIUM ALKALOIDS

Several alkaloids found in opium have great importance and wide use. Among these are **Morphine** and **Codeine**. These occur in the dried sap of



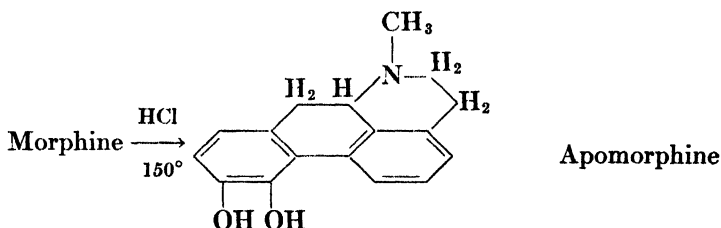
the poppy, along with gums, resins, sugar, protein matter, and about twenty other alkaloids. Neither morphine nor codeine has yet been synthesized; therefore the formulas cannot be considered as final.



Morphine (Gulland and Robinson). Codeine has the same framework with a methoxy group at (A) instead of hydroxyl. Diacetylmorphine is known as heroin.

Morphine is given for the relief of pain, very small amounts (about 0.01 gram or less) being effective. In larger doses it causes sleep. It is a habit-forming drug, the habit being very difficult to break. Codeine has a sedative action; it is less habit-forming than morphine, and is substituted for morphine in many cases.

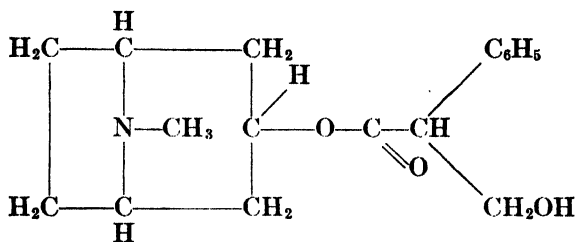
These alkaloids are seen to have the phenanthrene nucleus. Morphine when treated with concentrated acids loses a molecule of water and undergoes a profound structural change. Along with this change in structure we note a like change in action. Apomorphine, the new compound produced, is an effective emetic, useful in poisoning cases.



The National Research Council is sponsoring research at the National Institute of Health, with the object in view of replacing morphine with some synthetic compound which will have the valuable analgesic action of morphine, but avoid its habit-forming tendency. Valuable findings have already resulted from this study.

#### ATROPINE, COCAINE (CONDENSED PIPERIDINE-PYRROLIDINE ALKALOIDS)

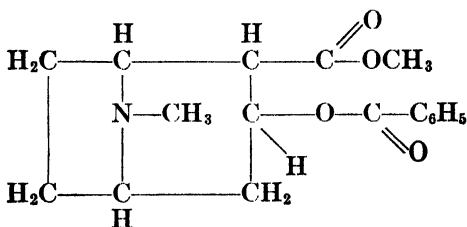
**Atropine** is contained in several plants (belladonna, henbane, thorn apple) in small amounts, being usually obtained from belladonna root. In nature it is racemic; along with it is found its *levo* isomer, hyoscyamine.



Atropine

Atropine is a violent poison, as little as 0.10 gram proving fatal. It acts as an anodyne and mydriatic, used principally in ophthalmic work to dilate the pupil of the eye, so as to allow a better examination of the interior.

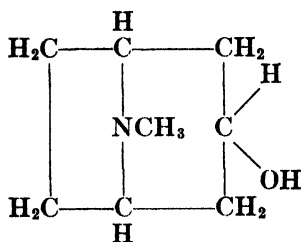
**Cocaine** proceeds from an altogether different source than does atropine, being extracted from the leaves of the coca tree; however, the two alkaloids are alike in structure, and hence in physiological action they somewhat resemble each other.



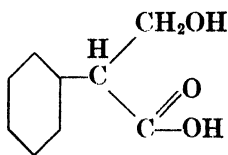
Cocaine

Cocaine is somewhat less poisonous than atropine. It is used as a local anesthetic and a mydriatic (to dilate the pupil of the eye). Cocaine is a habit-forming drug; its prolonged use leads to mental deterioration and insanity.

The hydrolysis of atropine yields tropine and tropic acid:

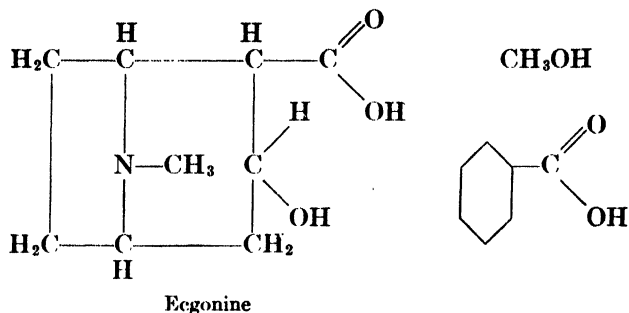


Tropine



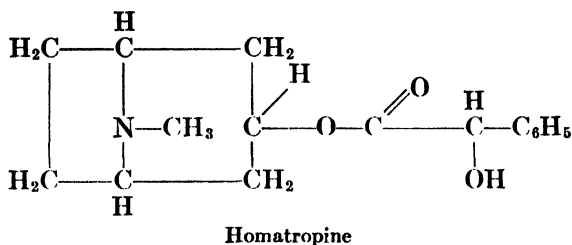
Tropic acid

whereas cocaine by hydrolysis splits into *l*-ecgonine, methyl alcohol, and benzoic acid:



ecgonine being a carboxy derivative of tropine.

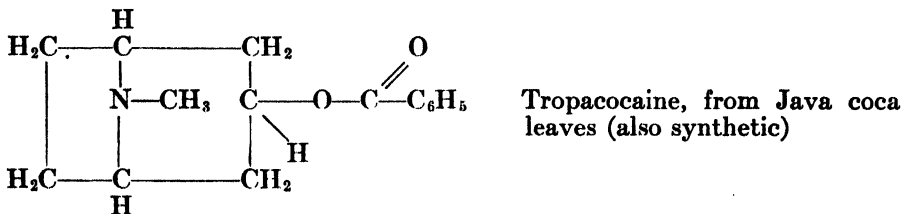
Various derivatives of tropine with acids have been prepared (the tropeines) some of which have mydriatic powers. Homatropine, a tropeine derived from mandelic acid (phenylglycolic acid) and tropine, is a substance of some value.



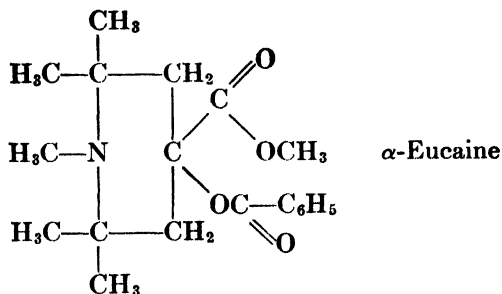
#### COCAINE SUBSTITUTES, ETC.

Solutions of cocaine when made up for hypodermic use have the disadvantage of being unstable and subject to spoilage; the toxicity of cocaine is also to be considered as a disadvantage. Various substitutes for cocaine have been offered with a view to preserving the physiological effects of cocaine, while avoiding the above named disadvantages.

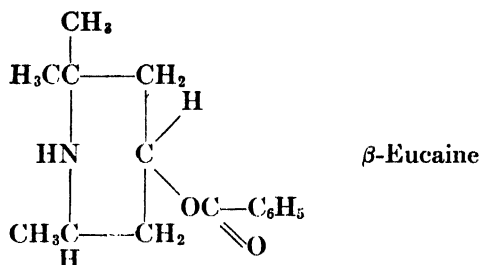
In several of these substitutes the general structure found in cocaine is retained; note the following compounds:



**Tropacocaine** is less toxic than cocaine, less subject to spoilage, and a stronger local anesthetic.

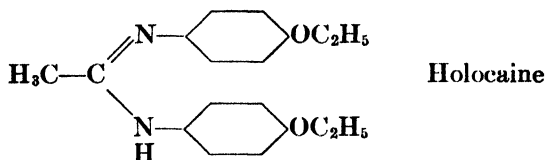


$\alpha$ -Eucaïne is less toxic than cocaine. As it is stable to boiling, its solutions may be sterilized. Its injection is, however, rather painful and irritating.

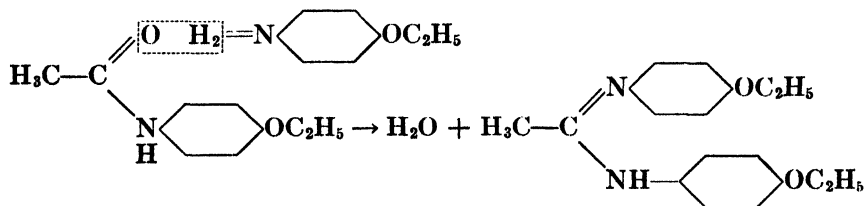


Like  $\alpha$ -Eucaïne, this substance is stable to boiling. It possesses equal anesthetic value to cocaine, but is less toxic.

Among other substances used for local anesthesia is:

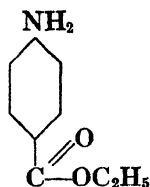


Synthesis of holocaine from phenacetin and phenetidine:

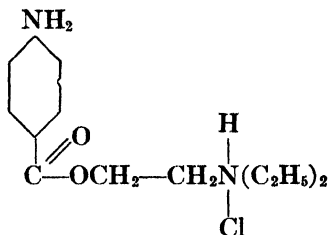


Holocaine is more toxic than cocaine. It is rapid in action and its solutions are stable.

Derivatives of aminobenzoic acid which are used as anesthetics are **Anesthesin** and **Novocaine**:

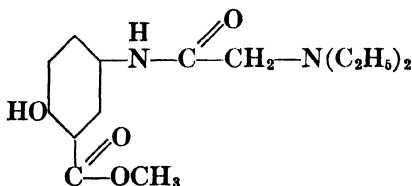


Anesthesin

Novocaine  
(Procaine)

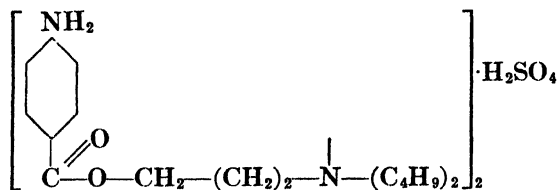
The efficacy in the anesthesin series rises with the weight of the ester radical, reaching a peak with the butyl compound (butesin). This is more than four times as effective as anesthesin. In butesin picrate we have a compound which combines antiseptic and anesthetic properties, much used in the treatment of burns.

**Novocaine** is a powerful local anesthetic of wide use. It is non-irritant and about one-seventh as toxic as cocaine. It is not habit-forming, gives stable solutions.



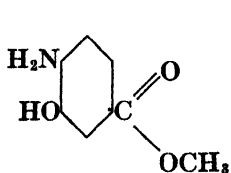
Nirvanine

**Nirvanine** resembles orthoform in its action, but is less toxic.

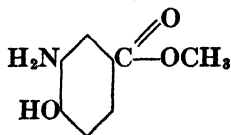


Butyn

**Butyn** has been used in the eye and nose and otherwise as a local anesthetic. It is more effective than procaine, and preferable to cocaine.



Orthoform



New orthoform

The orthoforms have both an anesthetic and an antiseptic action. They are used as dusting powders on wounds.

IRVING LANGMUIR. (American, 1881-

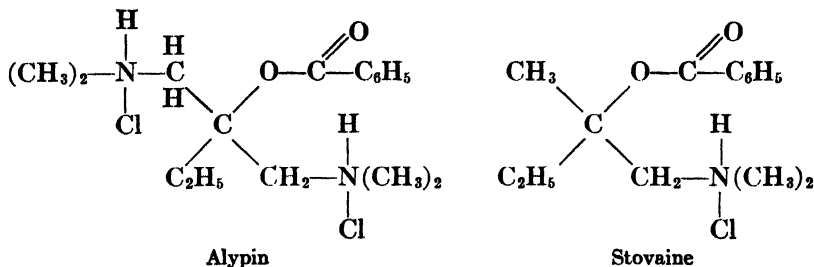
.) Langmuir's contributions to the theory of atomic and molecular structure have been of great importance in the recent development of organic chemistry. The atomic hydrogen flame, one of his inventions, is particularly pleasing to chemists, as is the argon-filled lamp. His work with molecular films will be valuable both in organic chemistry and biochemistry. He received the Nobel prize in 1932. Now associate director of the Research Laboratory of the General Electric Company. See *Ind. Eng. Chem. (News Edition)*, 10, 305 (1932)



FRIEDRICH BERGIUS. (German, 1884-

.) Industrial chemist. Inventor of processes for hydrogenation of coal and for making sugar from wood. He received the Nobel prize in 1931 for developments in high pressure synthesis. See page 42.

**Alypin** and **stovaine** are local anesthetics with action similar to that of cocaine. These substances, along with eucaine, have been superseded by novocaine and more recent compounds, but their formulas are included to show the trend of synthesis in this field.



Over two hundred alkaloids are known at the present time. Of these many have been so well studied that their structures are known, and some have been made synthetically. In addition to this many valuable substitutes have been prepared. The difficulty of the subject, and the practical and far-reaching benefits derived from new discoveries, make the study of alkaloids a fascinating field.

#### REVIEW QUESTIONS

1. Give a working definition of the term "alkaloid." Discuss the source of these compounds, and the methods which may be used to bring them into solution or to cause their precipitation.
2. Give an outline of the methods used to establish the structure of coniine.
3. Write equations for the synthesis of coniine.
4. Show by equations how piperonal may be synthesized from piperine and indicate by other equations the similarity of this synthesis to that from safrole.
5. What is the relationship between atropine and tropine? What are the tropeines?
6. Explain the synthesis of holocaine.
7. How might new orthoform be made from *p*-toluidine?
8. What would be formed by hydrolysis of the following compounds:  $\beta$ -eucaine, tropacocaine, homatropine, anesthesin?
9. What steps would you suggest to find the structure of a new natural alkaloid?
10. What similarity of structure exists between anesthesin, orthoform, and butyn?
11. What interesting researches on relationship of toxicity to molecular structure are suggested by inspection of the formulas of anabasine and nicotine?
12. Inspect the formula of piperic acid and suggest several reactions which it indicates. How might the compound be made from piperonal?
13. List by means of a chart the physiological effects of the natural and synthetic compounds mentioned in this chapter.
14. Predict the reaction of tropic acid with: (a)  $\text{PCl}_5$ ; (b) A dehydrating agent; (c) Concd. HI solution.
15. Name holocaine as a derivative of acetic acid.
16. Define the following terms: (a) Sedative; (b) Hypnotic; (c) Anesthetic; (d) Antiseptic; (e) Disinfectant; (f) Antipyretic; (g) Analgesic.
17. Indicate the asymmetric carbon atoms (if any exist) in the formulas of the following compounds: (a) Alypin; (b) Homatropine; (c) Tropic acid; (d) Ecgonine; (e) Quinine; (f) Nicotine; (g) Piperine.

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## CHAPTER XXXVI

### DYES

Although most of the groups we have so far studied are composed of colorless compounds, a few contain highly colored individuals whose shades range through all the gradations of the visible spectrum. Among these compounds we find the organic dyes. A dye is, to begin with, a colored substance, but to be practical it must adhere to cloth (leather, paper, cellophane, wood, etc.), and it should preserve its original appearance after repeated exposure to light, air, rubbing, and washing. Such a dye is termed "fast" in contradistinction to some which do not withstand such treatment, and which are accordingly called fugitive dyes. Dyes are used in inks and somewhat as pigments in paints. Certain selected dyes are used to color food products and candy.

Practically all dyes are organic compounds; this refers not only to the host of synthetic substances which have appeared in recent years, but also to those natural dyes employed by the ancients before the dawn of the science of chemistry.

However, not all colored organic compounds are capable of application as dyes. Certain well-defined structural relationships must exist within a dye molecule, and both the color of a compound and its ability to function as a dye are strongly affected by seemingly slight alterations of structure. Various structures which have dyeing properties will be presented in ensuing sections. Meanwhile, it will be of interest to consider the possible cause of color in a chemical compound.

### CAUSE OF COLOR

By passing white light through a prism, it is possible to split it into its components, which form what we call the spectrum of white light. If a part of this spectrum is blocked off and the remainder again collected by a lens, the resulting beam of light will be colored.

A portion of the spectrum might be stopped if we could have a system of resonators, tuned to vibrate at the same rate as the waves to be absorbed. An analogy is found in the piano or harp, in which a number of wires are arranged to vibrate at different rates. If a musical chord is sounded before the piano, those wires whose vibration rates correspond to the tones sounded will vibrate and absorb energy from the original sound, which will be so much weaker after passing the piano wires.

In the chemical compound, such a system of resonators might be found in the valence electrons, which are held in a state of tension between the atoms. If the natural vibration rate of certain electrons is that of a particular color of the visible spectrum, that color will be absorbed and the sum of the other colors of the spectrum will fall upon the eye. Thus, if the violet and blue rays are absorbed by a compound, it will appear in the complementary color yellow, and if the yellow and red end of the spectrum is absorbed, the compound will appear blue or green.

If the valence electrons of a compound are held with high tension, as in a saturated hydrocarbon, their natural vibration rate will be high and absorption of light, if any, will be in the ultraviolet region. Such a compound will appear colorless. If in some way the tension on the valence electrons can be loosened and the natural vibration frequency reduced, light of the visible spectrum may be absorbed, in which case the compound will appear to have color.

The valence electrons in unsaturated groups are less strongly held than in saturated unions. A compound containing such groups is apt to be colored. As the amount of unsaturation and the general complexity and the weight of a molecule are increased, the absorption tends to drift from the ultraviolet toward the red, and the color of the compound from no color through yellow, orange, red, violet, blue, indigo, to green. It is not yet possible to apply this information in a strictly scientific way but one can make a "practical" application in many cases. The possibility of resonance in dyes will be discussed later.

#### RELATION OF COLOR TO MOLECULAR STRUCTURE

The chemist has found that color in an organic compound depends upon the presence of certain groups, which are usually unsaturated in their nature. These are termed *chromophores*. The most important are:



Particular interest attaches to the grouping  $\text{:C—C:C—}\dot{\text{C}}$ : which is found in the quinone ring:



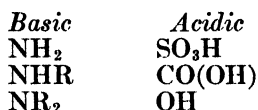
The quinone (quinonoid) ring, both *para* and *ortho*, exists as a part of many dye structures. In a colored compound, the part of the molecule which contains the chromophore is called a *chromogen*.

Not all of these chromophores are equally effective in producing color. We note that nitrobenzene is light yellow, and dinitrobenzene is no darker in color, while nitrosobenzene (melted) and nitrosodimethylaniline are green. Evidently, one NO group has greater effect than two NO<sub>2</sub> groups. Also, benzophenone is colorless, while thiobenzophenone, C<sub>6</sub>H<sub>5</sub>CSC<sub>6</sub>H<sub>5</sub>, is blue. In general, the color of a compound is deepened (becomes darker) by an

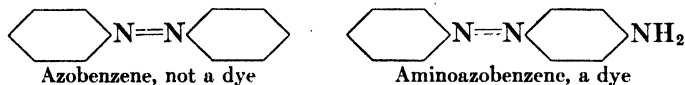
increase of molecular weight, especially by an increase in the number of chromophores. Also, the color of a dye is affected not only by the groups in the molecule but by their spatial relationship as well.\* A definite rule by which the exact color of a compound can be foretold by its structure has still to be formulated.

### COLORED COMPOUND VERSUS DYE

As has been said, an effective dye must be able to hold fast to cloth or other material. Many colored compounds are totally ineffective as dyes. To give dyeing properties, certain anchoring groups, known as *auxochromes*, must be present in the molecule. These fall naturally into two groups, the basic and acidic auxochromes:



An example of the effect of an auxochrome is seen in the case of azobenzene, which is a red compound but incapable of acting as a dye. It becomes a dye substance when NH<sub>2</sub> is introduced in the *para* position, forming aminoazobenzene:



Often, a colorless chromogen becomes colored upon introduction of an auxochrome. For example benzophenone, which is colorless, becomes yellow when NH<sub>2</sub> is introduced; nitrobenzene is much lighter in color than nitroaniline, etc. Certain auxochromes have higher effectiveness than others.† For modern interpretation of the function of auxochromes, see GILMAN, *Organic Chemistry* (Wiley, 1943), also BURY, *Auxochromes and Resonance*, *J. Am. Chem. Soc.*, **57**, 2115 (1935).

### GENESIS OF DYES

For the making of dyes, certain "original" substances are essential; these include benzene, naphthalene, anthracene, phenol, cresols, etc.—coal tar derivatives, which by various chemical processes (nitration, sulfonation,

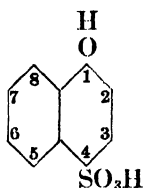
\* Spatial relationships are also very important in determining the odor or taste of organic compounds. (See footnote, page 763 and reading reference 25, page 708.)

† The original definition of an auxochrome group referred to its ability to deepen the color of the compound. The basic auxochromes have this ability, but the strongly acidic auxochromes do not.

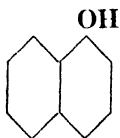
halogenation, alkylation, and the like) are converted into "intermediates." The intermediates are such compounds as will by simple reactions form the dyes.

Intermediates comprise: (1) Nitro compounds (nitrobenzene, nitroaniline, etc.); (2) Amino compounds (aniline, toluidine, naphthylamine); (3) Phthalic acids (anhydride, phthalimide); (4) Sulfonic acids; (5) Halogen compounds; (6) Phenolic compounds and aminophenols; (7) Aldehydes and carboxylic acids, and, (8) Derivatives having several functions within the molecule (mixed compounds).

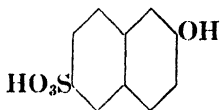
Several of the mixed derivatives of naphthalene which find application in the making of dyes are shown below.



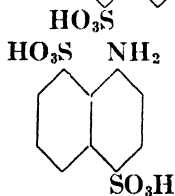
Neville and Winther's acid  
(231,165)



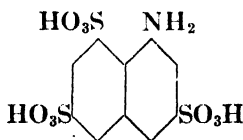
L acid  
(117,818)



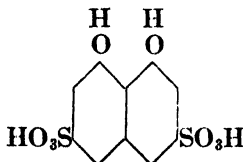
Schaeffer's acid  
(198,922)



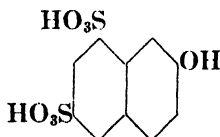
Schoelkopf's  
acid  
(398,827)\*



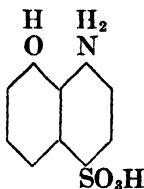
1-Naphthylamine-  
3,6,8-trisulfonic  
acid, Koch's acid  
(4,738,923)\*



Chromo-  
tropic  
acid



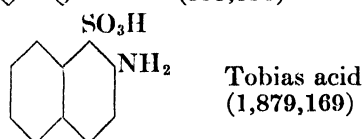
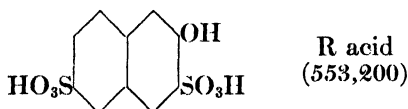
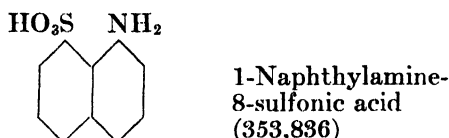
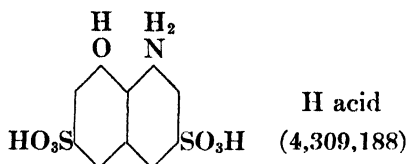
2-Naphthol-6,8-di-  
sulfonic acid  
(1,370,964)



S acid

Other compounds (1-naphthylamine-4,8-disulfonic acid, 1-naphthylamine-8-sulfonic acid, etc.) are also known as S acid.

\* Figure for 1939.



This list is in no sense exhaustive but will indicate the variety of compounds employed. The figures give the United States production in pounds for 1940.

### CLASSIFICATION OF DYES

Dyes are variously classified according to several distinct points of view. Those dyes which have NH<sub>2</sub>, NHR, or NR<sub>2</sub> group will form salts with acids, hence they are termed *basic dyes*, while those which possess such groups as SO<sub>3</sub>H, CO<sub>2</sub>H, or OH form salts with bases and are known as *acid dyes*. The classification which follows depends upon the way in which the dye is applied.

(1) **Direct Dyes.** These adhere directly to the cloth to be dyed without the aid of supplementary chemicals. Wool and silk dye more easily than does cotton. Both of the former are protein in nature and have NH<sub>2</sub> and CO<sub>2</sub>H groups in their molecules. For this reason they are salt-forming and can unite with a basic or acidic dye. Cotton (Rayon) has OH groups. These are exceedingly feeble acids, not effective in forming salts with dyes.

Dyes built upon certain specific nuclei (for example, the benzidine molecule) are direct for cotton. These are called *substantive dyes*. The reason for this selectivity is not known. Congo red and Benzopurpurin 4B are of this type. Such dyes are also direct for silk and wool; they are sometimes called *union colors*. Dyes sold for home use are often of this type. In direct cotton dyeing, sodium chloride or sodium sulfate is added to the dye bath in order to decrease the solubility of the dye and aid in exhausting the bath.

(2) **Adjective or Mordant Dyes.** These are unable to dye cloth directly, but may do so with the aid of a mordant.\* The mordants generally used comprise hydroxides or basic salts of aluminum, chromium, tin, or iron. These are able to form insoluble compounds with the dyes, and if the cloth is first dipped in a solution of the mordant, the insoluble dye-mordant compound is firmly fixed within the fiber as it forms.

\* It should be understood that the terms direct and mordant as applied here are relative. A dye may be direct for wool and silk but only able to dye cotton when mordanted (Malachite green), or may be direct for both animal and vegetable fibers, i.e., a substantive dye (Congo red).

Such substances as calcium phosphate or silica in finely divided state can adsorb dyes and function as mordants. Albumen similarly unites with dyes; the compound formed with the dye is fixed in the cloth by steaming, which causes coagulation of the albumen. Tannic acid is a valuable mordant for basic dyes.

To prevent the mordant from being washed out of the cloth prematurely, it is fixed by precipitation with a suitable fixing agent. Tartar emetic and stannic chloride are examples of chemical fixing agents. A piece of cloth mordanted with tannic acid has insoluble antimony tannate precipitated in the fibers after treatment with tartar emetic. This will then combine with and hold the dye. When a basic mordant such as an aluminum salt is used, the cloth is first dipped in the salt solution, and then steamed to cause hydrolysis, and consequent precipitation of aluminum hydroxide on the fiber.

Certain dyes give a variety of colors when treated with different mordants; they are called *polygenetic* dyes. Alizarin is an example. With an aluminum salt it gives a red compound, with ferric salts violet, with barium salts purple, etc. The colored insoluble compound formed from dye and mordant is called a *lake*. Some lakes are used as pigments.

(3) **Ingrain Dyes.** These dyes are actually formed within the cloth as the result of a chemical action between two substances, with which the cloth is successively treated. Examples are found in the field of azo dyes (see later sections).

(4) **Vat dyeing** is somewhat similar in principle to the above. Here the dye to be employed is insoluble in water, but by reduction yields an alkali-soluble compound\* with which the cloth is impregnated. Oxidation is then effected by exposure to air or by other means, and the insoluble dye is precipitated within the cloth. Indigo is applied in this manner. Its reduction product, indigo-white, which is alkali-soluble, is applied to the cloth and then oxidized to indigo.

### CHEMICAL CLASSIFICATION

The chemist finds it advantageous to classify dyes according to the nuclei about which they are built. This grouping is the most rational for one whose concern is the synthesis of dye compounds, rather than their practical use. In the following sections, representative compounds of the chief chemical groups are shown. It will not, however, be possible to show in each case the steps by which the formulas, which are those generally accepted, have been established.† Such material may be found in the more elaborate treatises of organic chemistry.

\* The reduced compound has enolic or phenolic hydroxyl groups; the sodium salts are water-soluble.

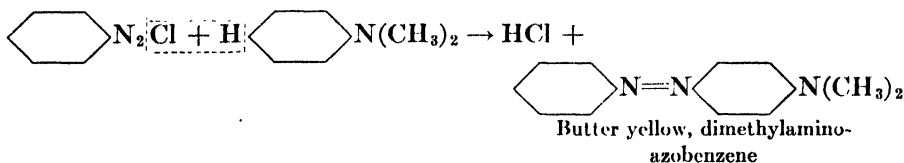
† Neither is it possible to show examples of all of the types of dyes which are actually in use. Most of the examples given have homocyclic ring systems, but many dye types with heterocyclic systems are known and used.

**Azo Dyes.** The nucleus of these dyes is azobenzene,



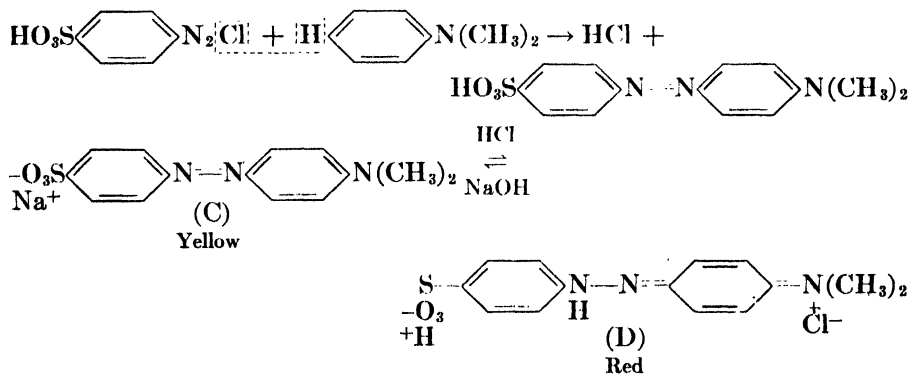
They are formed by the coupling of a diazotized primary amine with an amine or a phenol (naphthol). The reaction is discussed in Chapter XXV.

*Butter Yellow.* From aniline (diazotized) and dimethylaniline:



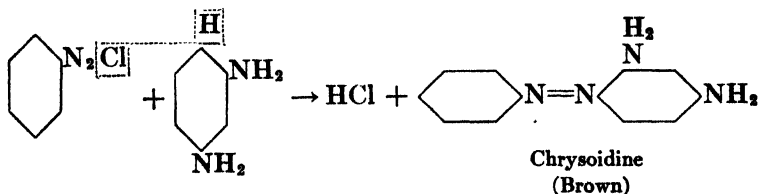
This dye is used to color butter, oils, as an indicator in the titration of gastric contents to determine free hydrochloric acid.

*Methyl Orange.* From diazotized sulfanilic acid and dimethylaniline:



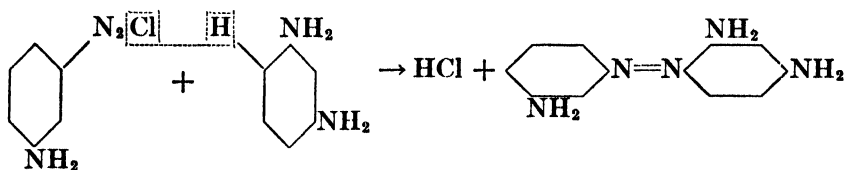
This substance is well known as an indicator, while not particularly useful as a dye. The change of color which occurs on addition of acid is due to a shift which introduces additional chromophores. Note that the deepening of color is associated with the change from benzene structure (C) to quinonoid structure (D). The reverse change may be brought about by the addition of alkali.

*Chrysoidine.* From aniline and *m*-phenylenediamine:

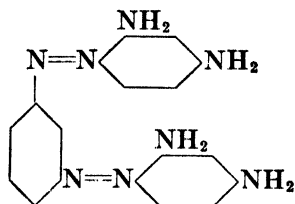


A direct dye for silk and wool. Cotton requires a mordant.

**Bismark Brown.** From *m*-phenylenediamine partially diazotized:



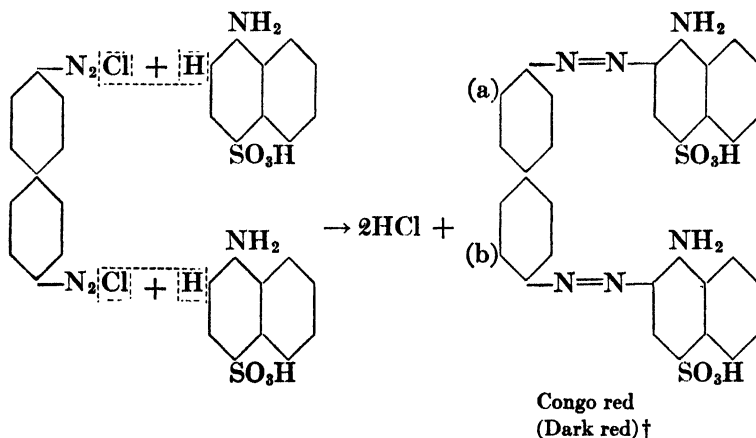
Some of the following compound is formed in this reaction, from molecules of the diamine in which both amino groups are diazotized:



Dyes a dark brown color. Used for leather, wool, mordanted cotton.

**Orange II** is an important dye. It is made from diazotized sulfanilic acid and *beta* naphthol. Coupling occurs *ortho* to the hydroxyl group, in the *alpha* position.

**Congo Red.** A polyazo dye, from benzidine disazotized\* (tetrazotized), coupled with 1-aminonaphthalene-4-sulfonic acid:



Congo red, like other similar dyes derived from benzidine, is a direct dye for cotton. It was the first of such dyes to be synthesized. Other Congo

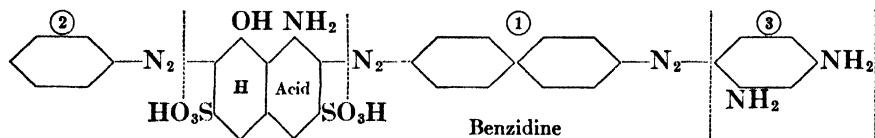
\* We have disazo-, trisazo-, and tetrakisazo dyes, with two, three, or four  $\text{—N=N—}$  groups respectively.

† Benzopurpurin 4B, an important direct dye, has a structure like that of Congo red, with methyl groups at (a) and (b). Over 800,000 pounds were made in this country in 1940.

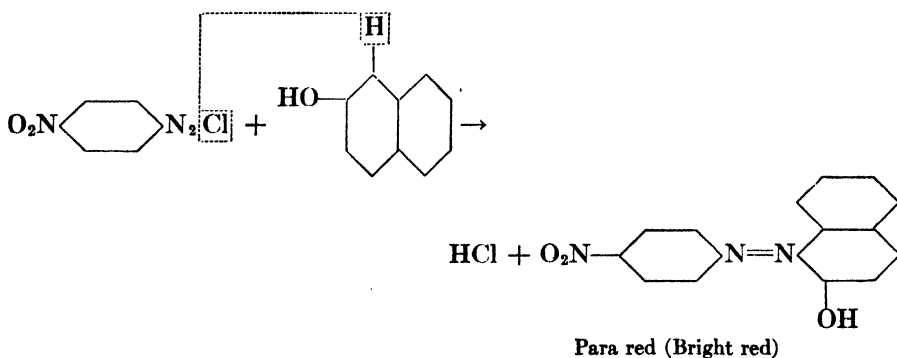


dyes are made from benzidine, tolidine,\* and similar compounds, tetrazotized and coupled with amino and hydroxy derivatives of naphthalene-sulfonic acids. The dyes are various shades of red and blue.

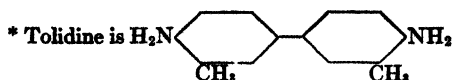
*Direct black EW* is a trisazo dye formed from H acid, aniline, benzidine, and *m*-phenylenediamine, through separate reactions of diazotization and coupling. The dotted lines in the formula mark off the locations of the beginning compounds, and the numbers show the order of the coupling.



*Para Red.* This is an example of an *ingrain dye*. The cloth is impregnated with an alkaline solution of  $\beta$ -naphthol, washed and dried, and then dipped into a solution of diazotized *p*-nitroaniline:



The reaction by which an ingrain dye is formed may be used to test for nitrites in water analysis. Thus, if sulfanilic acid,  $\alpha$ -naphthylamine, and a small amount of acetic acid are added to water containing nitrites, nitrous acid is released, and diazotization and coupling occur, with the production of a red dye. The depth of color, when compared with standards previously prepared from known nitrite solutions, allows an estimation of the amount of nitrites in the sample of water. Other applications of the coupling reaction, similar in theory to the nitrite test, are commonly employed in analytical work.

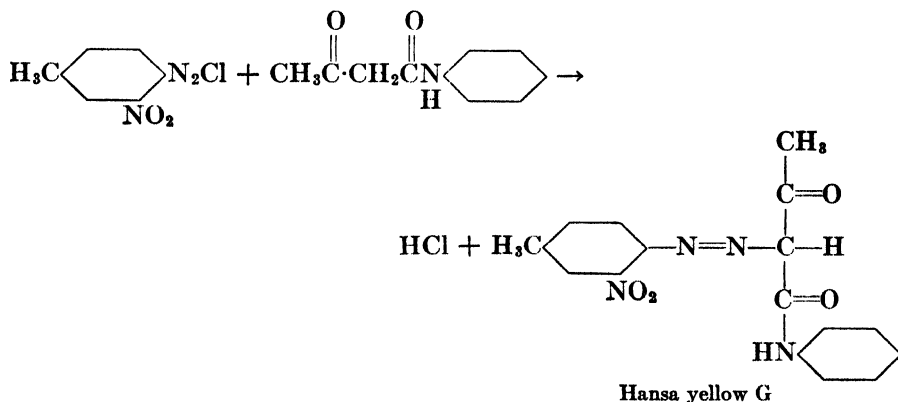


By coupling various diazotized compounds with *beta* naphthol, different colors are secured as follows:

<i>m</i> -nitroaniline.....	orange
benzidine.....	red-brown
dianisidine.....	blue
<i>o</i> -anisidine.....	red
$\alpha$ -naphthylamine.....	claret

The anilide of 3-hydroxy-2-naphthoic acid (Naphthol AS) is used as a second component for dyes and lakes as indicated for *beta* naphthol. A large number of dyes, with colors from yellow to black, are made in this way. *Developed dyes* are applied by a process which is the reverse of that just described. The cloth is soaked with an amino compound which is then diazotized upon the cloth. Contact with a suitable amine or phenol allows a coupling reaction to take place which yields the finished dye.

*Hansa Yellows.* Diazonium compounds can couple with acetoacetic ester or acetoacetanilide to give stable compounds. The Hansa yellows are made in this way.

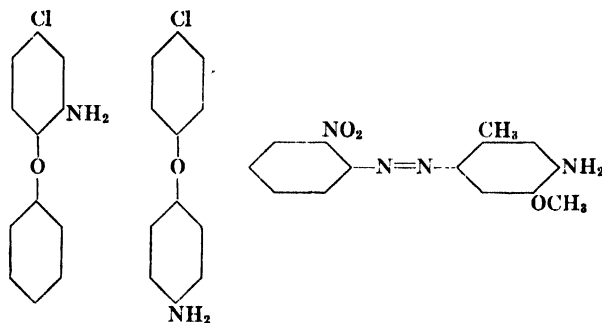


Various derivatives of nitroaniline are employed with acetoacetanilide and related compounds to make these dyes. They are brilliant yellow, alkali-fast dyes, especially useful for printing inks.

*Stabilized Diazonium Salts.* A technical difficulty in the use of azo dyes lies in the necessity for preparing the diazonium salt solution for each operation. This has been largely overcome by a variety of methods.

(1) The amine, sodium nitrite, and coupling component are mixed in the dry state. For use, the material is dissolved in water and printed on the cloth. When acid is added, nitrous acid is produced, and diazotization and coupling occur.

(2) Diazonium salts of certain structures are stable when dry, especially when diluted with neutral salts. Examples of amines which give such salts are:



Many other examples could be given.

(3) Double-salts which are stable can be formed with diazonium salts and other salts such as zinc chloride or stannic chloride.

(4) Mention was made on page 481 of the stable *antidiazotates* which may be made from diazonium salts. Such compounds may be mixed with coupling components, and marketed as stable powders or pastes. Under alkaline conditions little or no coupling occurs. After the paste is printed on the cloth an acid treatment releases the diazonium salt, which then couples and forms the dye in the fiber. The *antidiazotates* are called nitrosamines by practical chemists.

By these methods and others the dyer is supplied with stable diazonium compounds.

**Diazo Prints.** Certain diazo compounds are easily decomposed by light and are valuable for this reason. Paper coated with such a compound is covered with a traced drawing and exposed to light. The diazo compound is decomposed, except where protected by the lines of the drawing. Coupling with a suitable compound gives an azo dye deposit which duplicates the drawing. Many modifications of this basic idea are now in use.

Azo dyes are acid, basic, mordant, and direct (cotton). The ingrain dyes (ice colors) have particular importance due to their fastness of color. They are known in all shades from yellow to black.

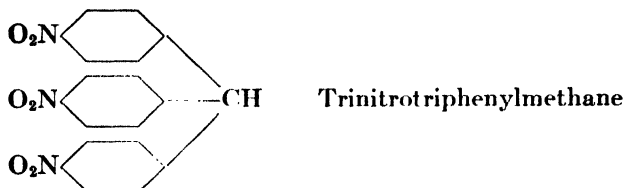
The ease of preparation of azo dyes and the possibilities for variation in dye structure have caused intensive research in this field. Many interesting and important reactions which could not be included here will be found in the references given at the end of the chapter.

**Triphenylmethane Dyes.** The nucleus of this group is triphenylmethane. Dyes of this group were the first to be thoroughly studied and synthetically prepared. The initial impetus came from the work of Perkin (1856), who in trying to prepare quinine from the oxidation of crude aniline with chromic acid, secured a red-violet dye, which he named mauve. This was the first synthetic dye;\* during the many experiments which followed this discovery, it was found by Verguin (1859) that mild oxidation of crude aniline with such agents as arsenic acid, nitrobenzene, or stannic chloride gave a red dye (Magenta, Fuchsin). Hofmann was later able to show that this dye was formed from aniline, *p*-toluidine, and *o*-toluidine, the latter being present as impurities in the crude aniline employed. A similar dye known as pararosaniline is a product of the oxidation of *p*-toluidine and aniline.

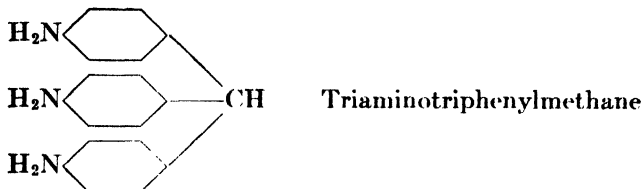
\* It would perhaps be better to say that this was the first synthetic dye whose formation led to useful developments in the dye industry. Wolfe in 1771 and Hausmann in 1788 had produced picric acid by nitric acid oxidation of indigo, and Runge in 1834 had made rosolic acid from phenol, which he noted in that same year as a component of coal tar.

**Study of Structure.** The structure of these dyes was established by the researches of Emil and Otto Fischer (1878) who showed that both are derivatives of triphenylmethane, magenta being the methyl homolog of pararosaniline. The latter may be synthesized as follows from triphenylmethane:

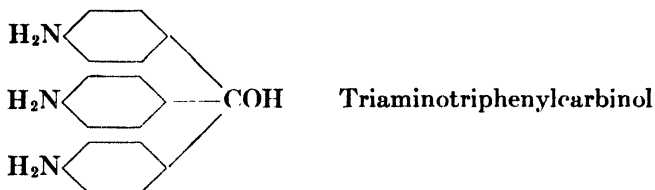
(1) Nitration of triphenylmethane by cold concentrated nitric acid causes the introduction of three  $\text{NO}_2$  groups *para* to the nuclear methane carbon atom:



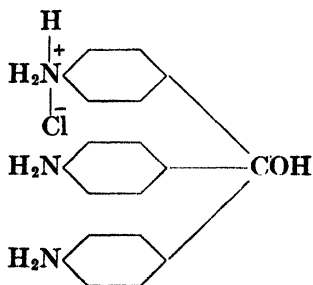
(2) By reduction, triaminotriphenylmethane is obtained:



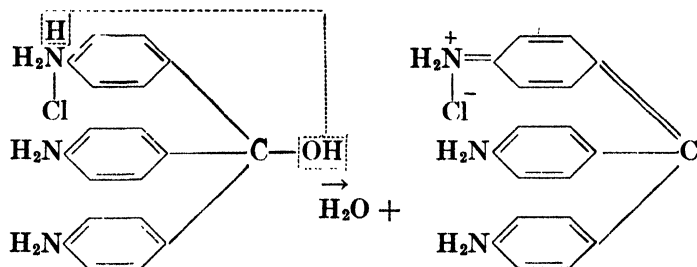
(3) Mild oxidation converts this compound to a derivative of triphenylcarbinol (note remarks on page 492).



This compound is properly called pararosaniline. It is colorless but upon treatment with acids, it forms salts which are colored, and which act as dyes. It is supposed that the acid attacks one  $\text{NH}_2$  group in the usual way, giving a salt:



The dye is formed by the loss of a molecule of water from this salt, and it is thought that a rearrangement takes place by means of which one of the benzene rings assumes the quinone form, thus increasing the number of chromophores:



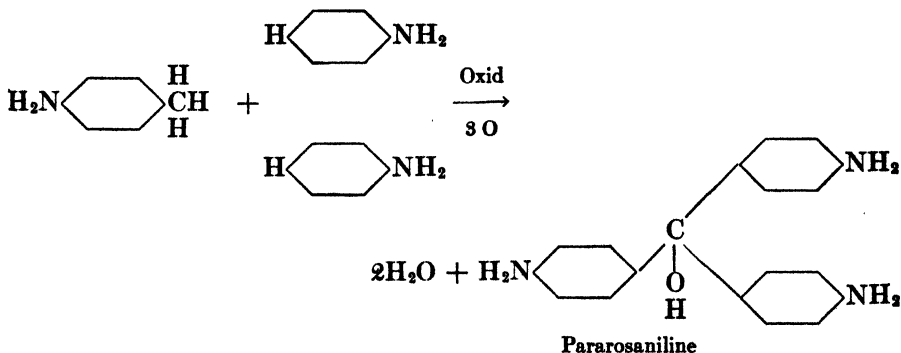
By the addition of a base, this series of changes may be reversed.

Triphenylmethane may be formed from pararosaniline by first reducing it to triaminotriphenylmethane, subsequently removing the amino groups through diazotization, etc.

**Resonance of Triphenylmethane Dyes.** We have arbitrarily assigned the quinone structure to the upper ring in the formula next above, but the student will note that the three rings are equivalent and that any one of them could assume quinone structure. A situation of this kind produces a resonating molecule (page 398). The deep colors of the triphenylmethane dyes are presumed to be caused by this resonance.

We may say, then, that the function of the auxochrome in a dye is to permit the possibility of resonance. We note in support of this idea that the compound  $\text{HN}=\text{C}_6\text{H}_4=\text{C}(\text{C}_6\text{H}_5)_2$  is colorless, whereas  $\text{ClH}_2\text{N}=\text{C}_6\text{H}_4=\text{C}(\text{C}_6\text{H}_5)(\text{C}_6\text{H}_5\text{NH}_2)$ , which has the same chromophore, is a dye (Döbner's Violet). The latter compound has a structure which permits resonance to occur. Dyes belonging to other series can also be shown to have resonating structures.

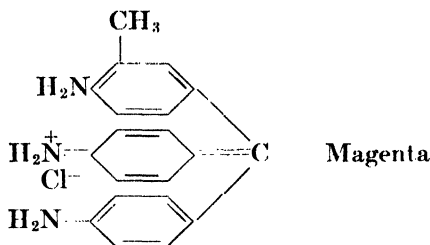
**Synthesis.** Pararosaniline is formed when a mixture of *p*-toluidine and two parts of aniline is oxidized with nitrobenzene.



The other dyes of this group are formed from triphenylcarbinol derivatives similar to pararosaniline, by the action of acids. The colorless carbinol

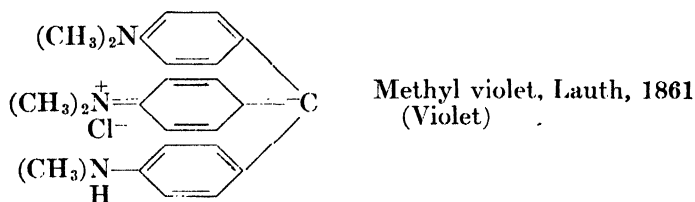
compounds are called "color bases." Their triphenylmethane reduction products, which also are colorless, are termed "leuco bases."

*Magenta* (Fuchsin) as stated is a homolog of pararosaniline (salt):

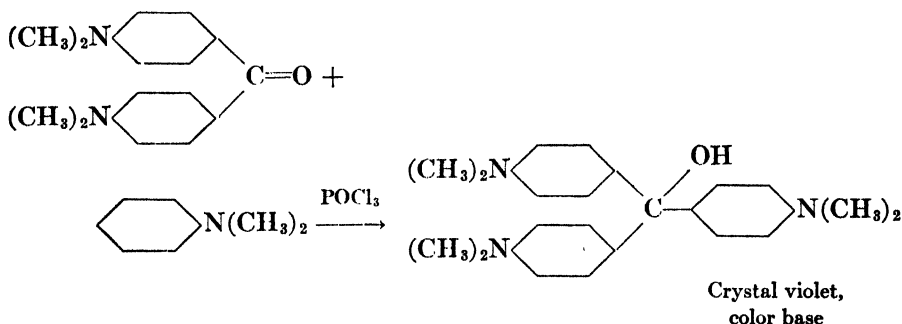


Its color base is called rosaniline. The dyes of rosaniline and pararosaniline are red. They are still in use.

*Methyl Violets.* The methylation or ethylation of the amino groups of pararosaniline yields violet dyes. Methyl violet is the pentamethyl derivative.

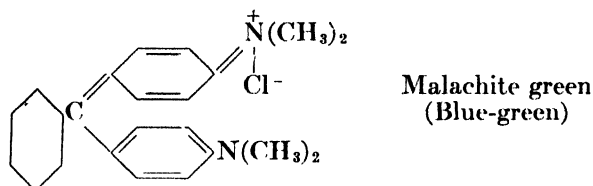


*Crystal violet* has six methyl groups. It is formed by the condensation of Michler's ketone (page 472), with dimethylaniline:



The alkylation or arylation of the amino groups of magenta causes a deepening of color. The effect depends upon both the number and size of the groups, the color deepening from red of the unsubstituted dye to deep blue for the triphenylated dye. The methyl violets give beautiful color effects with silk, wool, and cotton. Silk and wool dye directly, cotton is mordanted with tannic acid and tartar emetic. These violets are used in indelible inks and pencils, for stamp pads, as indicators.

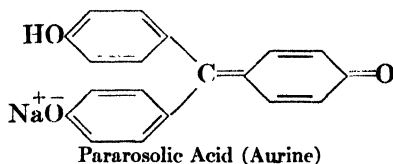
*Malachite green*, a green dye and stain, is formed by the condensation of benzaldehyde and dimethylaniline (equation, page 552), with subsequent oxidation and salt formation:



Malachite green dyes silk, wool, and cotton a blue-green color. Conditions of dyeing are as for methyl violets. In this dye the removal of one of the *para* dimethylamino groups is responsible for the change of color to green. (Note discussion of resonance, page 398.)

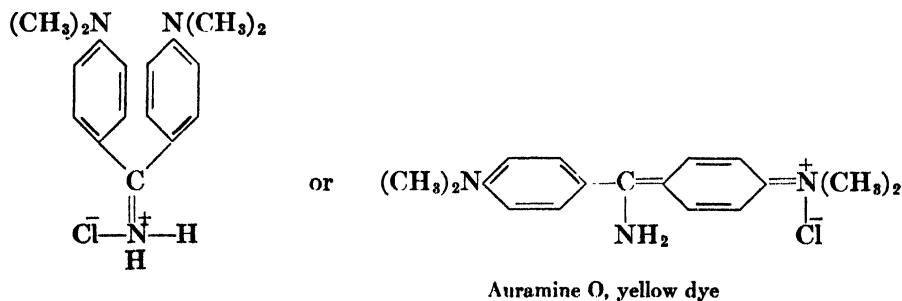
Furaldehyde, a substance of constantly growing importance, is able to form dyes in a manner analogous to that shown for benzaldehyde. See Reference 10, page 707.

*Pararosolic acid* and *Rosolic acid* are compounds with structures identical with those of pararosanine and rosanine, the  $\text{NH}_2$  groups of the latter being replaced by OH groups. They may, in fact, be prepared from the corresponding  $\text{NH}_2$  derivatives by the diazo reaction. Ordinarily, pararosolic acid is prepared from phenol, heated with oxalic acid and sulfuric acid, or from phenol and carbon tetrachloride.



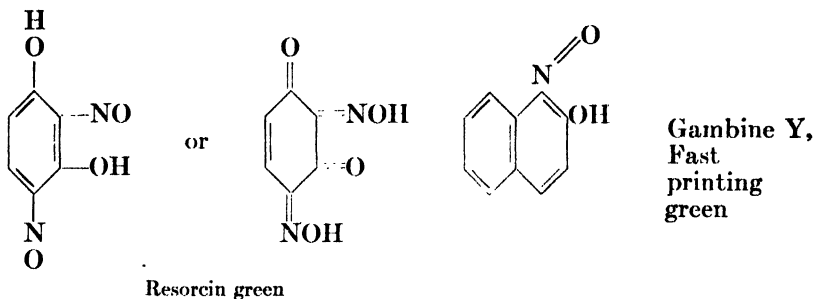
These compounds are not particularly useful as dyes.

**Diphenylmethane Dyes.** This is a small group. Auramine O is the most important example. It is made by action of Michler's ketone upon ammonium chloride and zinc chloride.

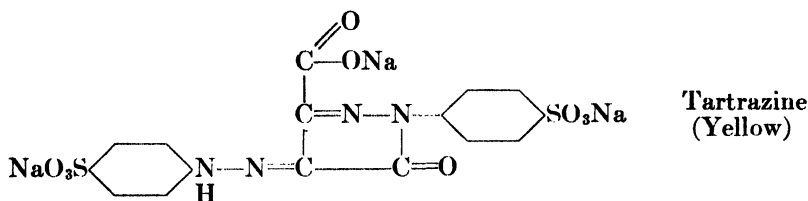


Auramine O is used for paper, silk, and cotton. It is a most powerful anti-septic, ranking higher than most dyestuffs, acting against a great many different organisms.

**Nitroso and Nitro Dyes.** Picric Acid (dye and explosive) has already been mentioned (page 509). Naphthol Yellow and Martius Yellow (page 588) are also representatives of nitro dyes. Resorcin Green is a nitroso dye. Gambine Y is another example, made from  $\beta$ -naphthol and nitrous acid.

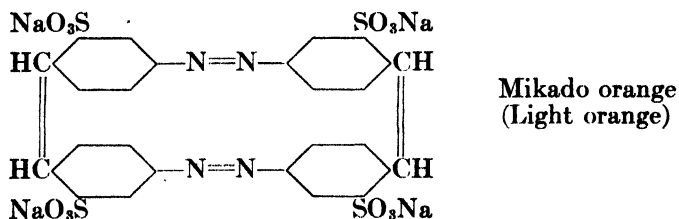


**Pyrazolone Dyes.** The best known of this series is Tartrazine, discovered in 1884 by Ziegler.



This is employed as a dye and food color. It is made from dihydroxytartaric acid and two moles of phenylhydrazine *p*-sulfonic acid.

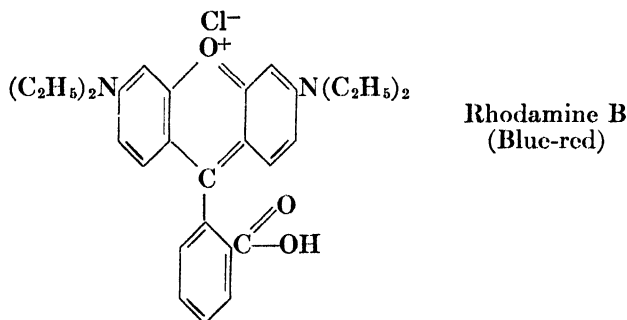
**Stilbene Dyes.** Among the better known derivatives of stilbene (diphenylethylene) is Mikado orange:



Mikado orange is made by reduction of dinitrostilbene disulfonic acid.

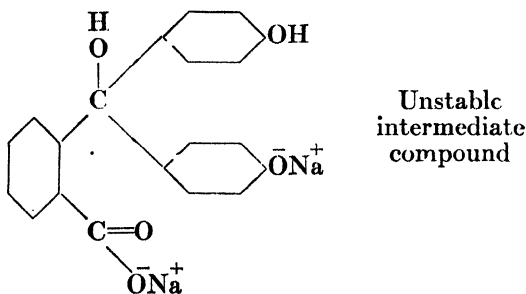


**Rhodamines.** The rhodamines are bluish-red fluorescent dyes.

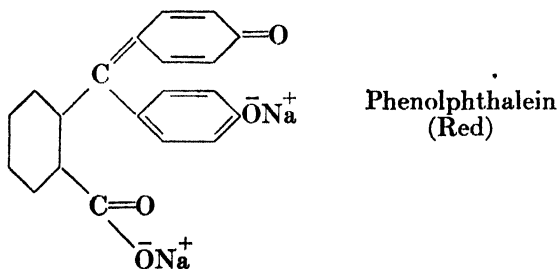


The rhodamines are amino derivatives of the phthaleins shown below. Rhodamine B is made by condensation of phthalic anhydride with *m*-diethylaminophenol.

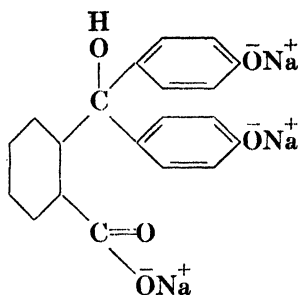
**Phthalein Dyes.** Phthaleins are derivatives of phthalic anhydride with phenols. Phenolphthalein is formed with phenol (equation on page 535). This compound is colorless, but when treated with a base the anhydride group is opened and a salt is formed:



It will be noted that this compound is a derivative of triphenylcarbinol. By loss of water and rearrangement of the molecule, this forms a red compound. The cause of color is presumed to be connected with resonance of the negative ion shown herewith.

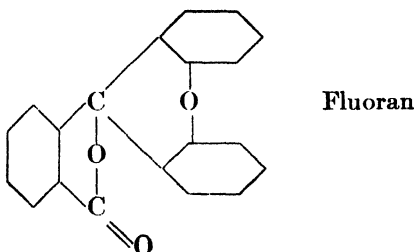


The addition of acid reverses these reactions, whereas with a large excess of base the following colorless compound is formed:



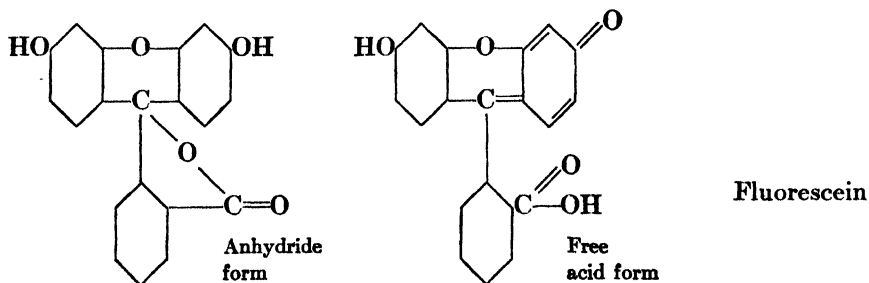
As phenolphthalein undergoes these changes with a very slight excess of  $\text{H}^+$  or  $\text{OH}^-$  ion, it is useful as an indicator. It is not a dye. Other uses of this substance are indicated on page 535.

If, in the reaction between phthalic anhydride and phenol, the attack takes place in the positions *ortho* to  $\text{OH}$ , we obtain Fluoran:



In the formation of this compound, a molecule of water is also lost between the two  $\text{OH}$  groups. Derivatives of fluoran give fluorescent solutions in alkali, as do many other compounds which contain an oxygen-carbon ring.

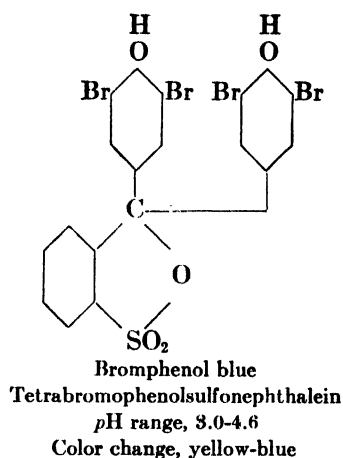
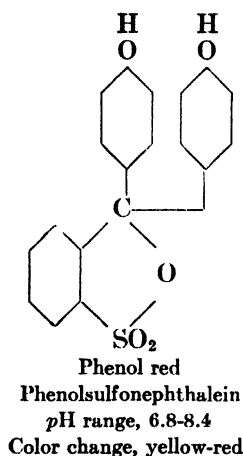
*Fluorescein*, product of the reaction of phthalic anhydride and resorcinol, is a fluoran derivative (dihydroxyfluoran). The compound gets its name from the beautiful yellow-green fluorescence of its alkaline solution. Fluorescein is mixed with other dyes to impart the fluorescent effect. Note that mercurochrome (page 608) is a derivative of fluorescein.



*Eosin*, the disodium salt of tetrabromofluorescein, is used as a dye for silk, wool, and paper, also in making red ink. It dyes a fluorescent pink. The compound is made from the action of bromine upon fluorescein dis-

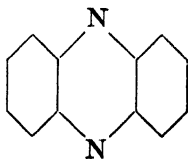
solved in alcohol. By varying the nature of the halogen, and by halogenation of the phthalic anhydride ring, a number of dyes (Rose Bengale, Phloxin, etc.) are made.

**Sulfonephthaleins.** These compounds, which have a structure similar to the phthaleins, are derivatives of sulfobenzoic anhydride (page 527). Phenol Red and Bromphenol Blue are representative members of the group, used as indicators.



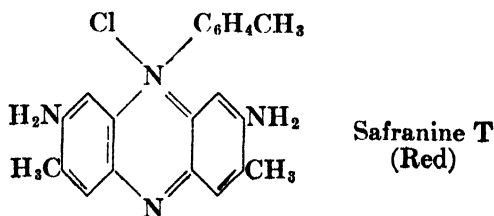
Phenol red is used to test the renal function. It is injected intravenously; 65-80% is excreted in one hour by a normal kidney; delayed excretion indicates abnormal conditions.

**Azine Dyes.** In azine dyes we have the nucleus

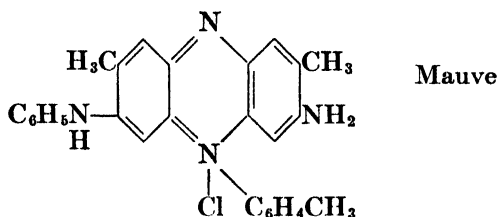


In Oxazine and Thiazine dyes, one of the nitrogen atoms is replaced by O and S, respectively.

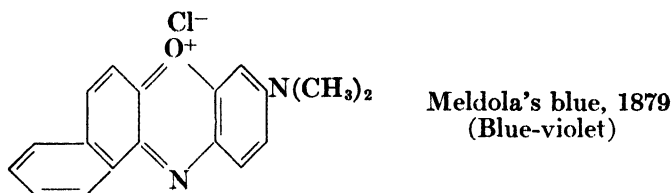
*Safranine* (Azine dye).



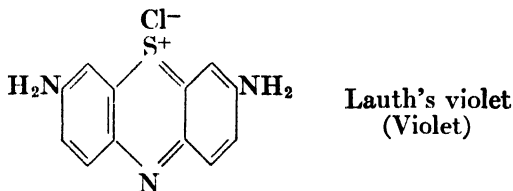
*Mauve*, *Mauveine*, which has been cited as the first synthetic dye, is an example of an azine dye.



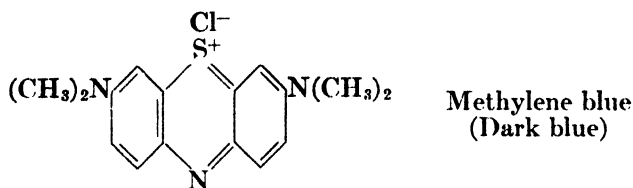
*Meldola's Blue* (Oxazine dye).



*Lauth's Violet*, Thionine (Thiazine dye), used as indicator and stain.



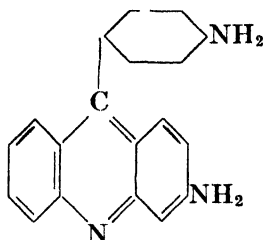
*Methylene Blue* (Thiazine dye).



These dyes are formed by condensation reactions of amino and hydroxy compounds, followed by oxidation. The sulfur of the thiazines is introduced by the use of sodium thiosulfate or a similar salt.

Methylene Blue is used as a dye and stain, and as a remedy for gonorrhea and rheumatism.

**Acridine Dyes.** These are derivatives of acridine (see page 654).

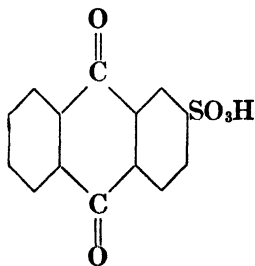
*Chrysaniline.*

Chrysaniline (Yellow)  
For cotton and leather

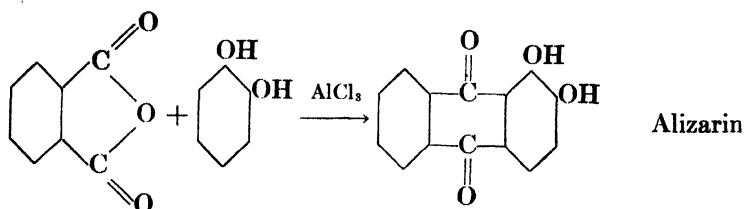
**Anthraquinone Dyes**, nucleus anthraquinone. One of the best known mordant dyes of this group is alizarin, which was formerly obtained from a glucoside, ruberythric acid, found in madder root. It is a mordant dye, and is polygenetic. The structure of this dye was determined by the researches of Graebe and Liebermann (1868), who also effected its synthetic preparation.

The following facts establish the structure of alizarin. (1) It is assumed to be dihydroxyanthraquinone from the formula established by analysis, and the fact that it yields anthracene when distilled with zinc dust. (2) It can be made from the condensation of phthalic anhydride and catechol; this shows that the two OH groups are on the same ring and in *ortho* position to each other. (3) It forms two mononitro compounds. In each of these the nitro group is on the same ring which holds the OH groups. If the hydroxyl groups were in 2-3 position, only one nitro compound could be formed, hence they must be in the 1-2 position.

Alizarin is prepared by the sulfonation of anthraquinone, which produces anthraquinone-2-sulfonic acid:

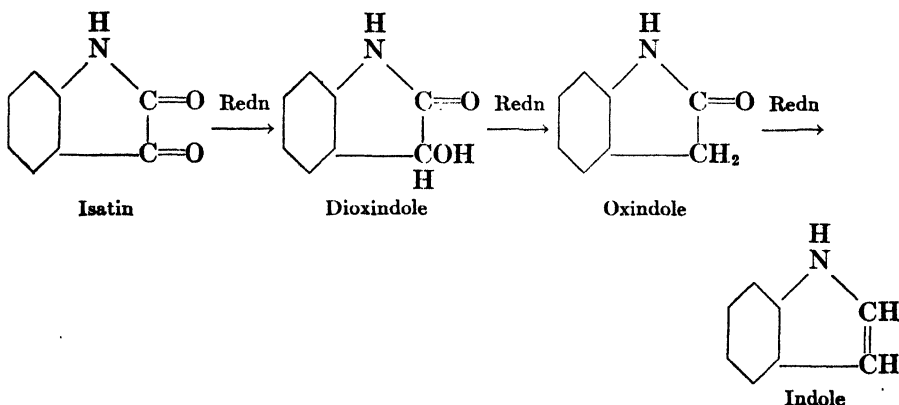


This compound, by fusion with sodium hydroxide and chlorate, is converted to alizarin. The additional hydroxyl could be secured by air oxidation, which occurs during alkaline fusion, but the use of the sodium chlorate speeds the process and prevents any reducing effect from free hydrogen. The formation from phthalic anhydride and pyrocatechol has been mentioned:

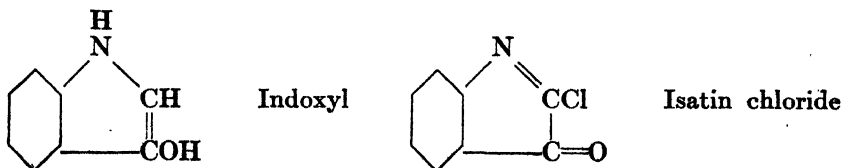


Other ways of making alizarin are known. For instance: the condensation of phthalic anhydride with chlorobenzene gives 2-chloro-anthraquinone; this is then fused with sodium hydroxide. Many other hydroxyanthraquinones are dyes. One of interest is 1,2,4-trihydroxyanthraquinone or purpurin. This, like alizarin, is found in madder. It can be formed from alizarin by oxidation with  $\text{MnO}_2$  and sulfuric acid. Mordanted with aluminum salts it gives a scarlet red color. Anthraquinone vat dyes, page 695.

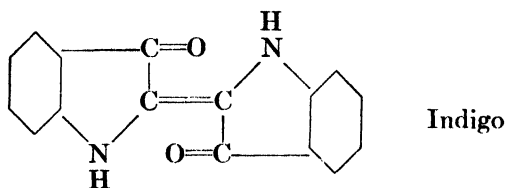
**Vat Dyes.** Of this group of dyes the best known member is indigo. In nature indigo occurs in the glucoside indican, which was formerly obtained from the stalk and leaves of *indigofera tinctoria*, also from the woad plant. The structure of the dye and its first synthesis were both worked out chiefly by Baeyer and his students, in a series of researches which consumed many years. It will be impossible for us to follow either of these in detail. Briefly, the oxidation of indigo gives isatin, a substance whose structure is shown by its progressive reduction, which yields indole; dioxindole and oxindole are intermediate products.



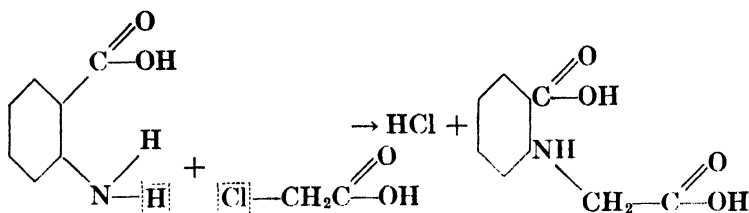
Indoxyl, an isomer of oxindole, gives indigo upon oxidation; also, isatin chloride,



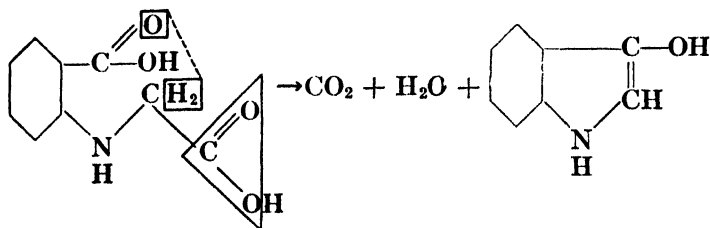
on treatment with zinc and acetic acid yields indigo, whose structure has been proved in this and other ways:



**Synthesis of Indigo.** Many syntheses are known for indigo, of which but two will be presented. One begins with the conversion of phthalimide or of phthalamic acid to anthranilic acid by the use of sodium hypochlorite (Hofmann reaction). The anthranilic acid is converted to phenylglycine-*orthocarboxylic acid* by treatment with chloroacetic acid:



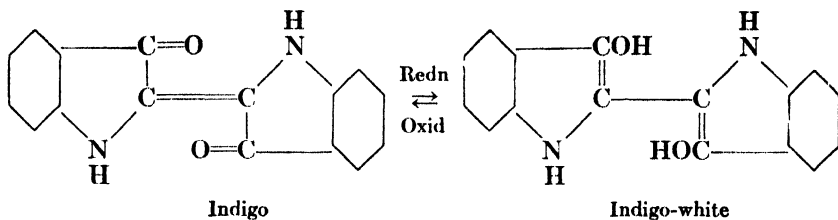
Fusion of this compound with sodium hydroxide and sodamide yields indoxyl, by loss of one mole each of water and carbon dioxide:



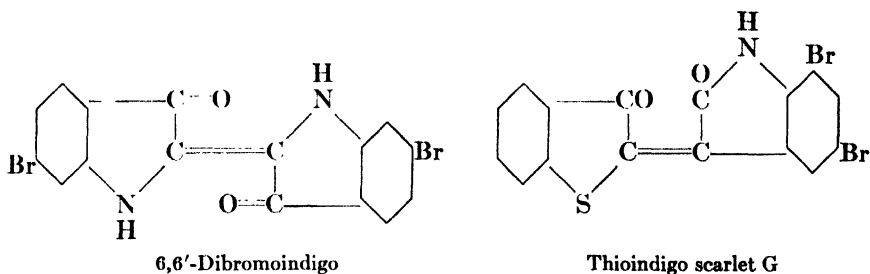
The oxidation of indoxyl gives indigo.

A better method than the one above, and the most important of the indigo syntheses, involves the following steps: (1) Reaction of aniline and chloroacetic acid to give phenylglycine. (2) Fusion of phenylglycine with sodium hydroxide and sodamide to yield indoxyl. (3) Oxidation of indoxyl to indigo.

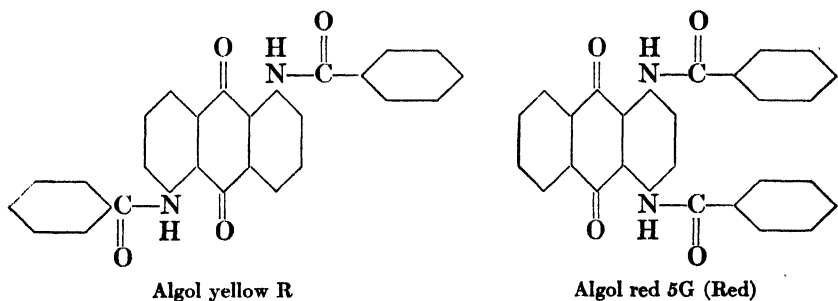
Indigo is reduced to colorless indigo-white, which is soluble in alkali. The cloth after being soaked in this solution may be exposed to air for reoxidation of the indigo-white to indigo.



Derivatives of indigo include halogenated compounds, and others in which sulfur atom has taken the place of nitrogen. Dibromindigo is interesting. This is the compound responsible for the dyeing effect of the famous Tyrian Purple obtained from the snail *Murex brandaris*. Thioindigo scarlet is an example of a sulfur derivative.



**Anthraquinone Vat Dyes.** The important group of Algal dyes was developed in Germany to compete with another group of vat dyes, the indanthrenes (also of German invention but from a different company). Examples are Algal Yellow R and Algal red.

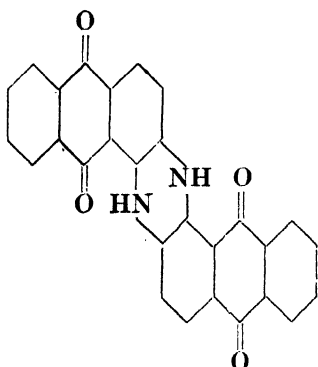


These dyes are obtained by the action of benzoyl chloride upon the corresponding aminoanthraquinones. They are reduced by sodium hydro-sulfite, hydroxyl group taking the place of the ketone oxygen, and in the reduced form are soluble in base. The cloth is soaked in the solution and exposed to air for reoxidation to the dye.

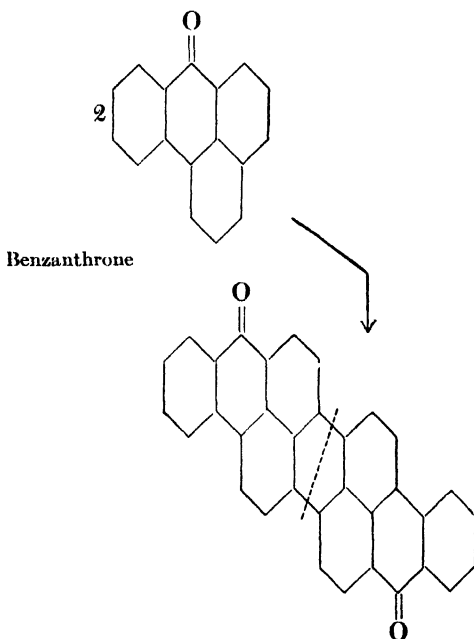
**Indanthrene Vat Dyes.** There are many examples of this type of dye, the formulas of which are usually somewhat complex. Indanthrene blue



**R** is made by alkali fusion of *beta* aminoanthraquinone; two molecules condense to form the dye.



Indanthrene blue R (Bohn)  
(Dark Blue)



Indanthrene Violet R (Violet)

Indanthrene violet R is made from benzanthrone (two molecules) by alkali fusion of halogenated benzanthrone. The dotted line shows where union occurs.

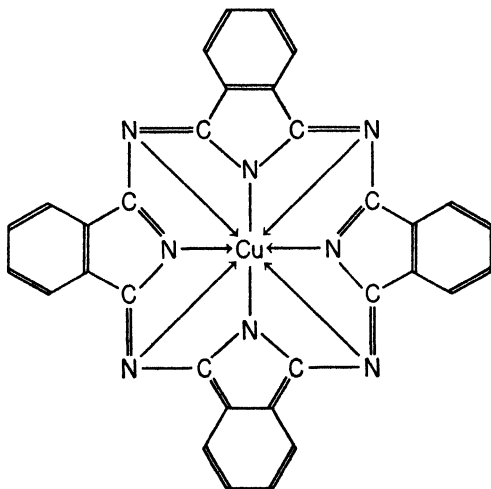
The vat dyes and ingrain dyes are fast, since they are quite insoluble in water. Their method of application, either from coupling of water-soluble units or from soluble leuco compounds, allows the use of large molecules. A direct dye must be water-soluble; if the molecule is large, solubilizing groups (salt-forming) will be needed, and the same water-solubility which aided in the initial dyeing will make it possible for the cloth to lose its color. Vat dyes have another advantage in that their application is not so complex as that of mordant or ingrain dyes.

**Sulfur Dyes.** The original dyes of this series were made by heating cellulose waste (sawdust, etc.) with sodium sulfide. They are now made from sodium sulfide or polysulfide or sulfur and various amines and phenols. The dyes are insoluble and are applied like vat dyes; that is the dye is dissolved with the aid of sodium sulfide or sodium hydrosulfite (hyposulfite), which causes reduction. After the cloth is soaked with the solution it is exposed to air. These dyes are fast to light and washing, and have the added virtue that they are cheap. They form an important group. Colors

are dark (black, blue, brown, green). No formulas are offered since in most cases they are unknown. Sulfur black, made from 2,4-dinitrophenol, is the chief member of the group.

Primuline is a mixture of several dyes made by first heating *p*-toluidine and sulfur, then sulfonating the resulting compounds. The dyes have free amino group; in practice primuline is diazotized and coupled with various phenols, etc., to form ingrain dyes.

**Phthalocyanine Dyes.** These dyes have a complex chromophore similar in structure to the framework of chlorophyll and hemin (page 704). Copper phthalocyanine is made by treatment of *o*-phthalonitrile with cuprous chloride or copper. Other metals may be used in a similar way.



Copper Phthalocyanine

The compounds of this series are green or blue; they are very stable to heat, also to acids and bases. They are widely used as pigments in printing inks, paints and lacquers, also somewhat as dyes. Metal-free phthalocyanines are easily made; halogenated and sulfonated phthalocyanines have been prepared. The latter give water-soluble salts suitable for dyeing.

#### THEORIES OF DYEING

Several theories bearing on the mechanism of dyeing action have been proposed, no one of which has had a complete ascendancy. Among these are: (1) *Colloidal theory*. This states that the dye and the cloth are colloids, oppositely charged, and that they mutually precipitate each other. (2) *Solution theory*. According to this theory the dye is presumed to be held in the cloth in solid solution. (3) *Chemical theory*. This theory assumes simply that the dye and the cloth form a chemical compound by the interaction of specific groups. (4) *Mechanical theory*. The mechanical theory assumes that in dyeing, the dye is mechanically held (adsorbed) in the fiber pores of the cloth. There is, of course, no set reason why one

explanation must fit all types of dyeing, nor is it impossible that in a given case two or more of these theories should apply. Thus dyeing might involve two steps, first an adsorption, and second the formation of a compound between fiber and dye.

### INDICATORS

The addition of acid to methyl orange or pararosaniline, which have basic groups, was seen to have the effect of deepening the color of the compound during salt formation, because of a shift or rearrangement of the molecule; a similar effect was indicated for the addition of a base to phenolphthalein, a potentially acidic compound.

This change of color may be used as an indication of the change from alkaline to acid solution in a titration, provided that the colored compound is sensitive enough to undergo the rearrangement quickly in the presence of a very slight excess of  $H^+$  or  $OH^-$  ion. Compounds so used are called indicators. Phenolphthalein, methyl orange, congo red, alizarin, various sulfonephthaleins, and other compounds are used in this way. The color changes of these and other indicators occur within certain narrow ranges of  $H^+$  ion concentration, both above and below  $pH$  7.

Indicators are now available for the entire  $pH$  range, and their use has greatly aided the chemist in many practical problems.

### USES OF DYES

Besides their primary function as color bearers, many dyes also find other uses. Those which possess nitro groups may function as explosives (picric acid is an example). Some are used as antiseptics (picric acid, brilliant

TABLE 45.—U.S. PRODUCTION OF CRUDES, INTERMEDIATES, AND DYES\*

	1936 produc- tion in thou- sands of gals. or lbs.	1940 produc- tion
Coal tar, gallons.....	560,386	673,287
Benzene, gallons.....	19,413	36,556
Toluene, gallons.....	19,807	30,440
Xylene, gallons.....	4,216	5,646
Naphthalene, pounds.....	89,536	159,637
Intermediates, pounds.....	509,706	805,807
Dyes, pounds.....	119,523	127,834

\* Compiled from reports of the U.S. Tariff Commission.

green\*) and as drugs (phenolphthalein, methylene blue). Their use as indicators has been mentioned, also the use of dye lakes as pigments in

\* Brilliant green is related to malachite green, having ethyl groups instead of methyl, and salt formation with sulfuric acid.

GUSTAV EGLOFF. (American, 1886-

.) Egloff's work has been chiefly concerned with petroleum: its origin, its refining, and its possible chemical transformations. He holds many patents on petroleum processing and has written hundreds of papers on petroleum technology. He is author or co-author of: *Earth Oil, The Reactions of Pure Hydrocarbons, The Physical Constants of Hydrocarbons, Catalysis, Emulsions and Foams*. Egloff is now director of research of the Universal Oil Products Company.



FRANK C. WHITMORE. (American, 1887-1947.) Author of the American Chemical Society monograph on mercury compounds and of the well known advanced organic chemistry text. Work with aliphatic compounds, rearrangements, mercury compounds, Grignard reagents, neopentyl compounds, polymerization. Formerly dean of the School of Chemistry and Physics in the Pennsylvania State College.

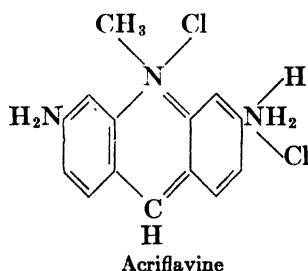
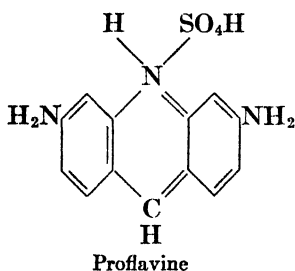
paints, printing inks, and lacquers. Dyes of the cyanine series, derivatives of quinaldine (2-methylquinoline) are used as sensitizers in photography. Their function is to increase the sensitivity of the photographic film to certain wave lengths of light, particularly in the red and infrared regions of the spectrum.

In the field of bacteriology and histology, dyes are useful for "staining." Dyes used in this work show a selective action towards tissue, staining some types of cells and not others. With bacteria, similar effects are observed. The stained tissues and germ cultures are much more easily differentiated under the microscope than they would be if uncolored.

This specific action of dyes toward certain organisms is said to have led to the search for compounds of arsenic similar in structure to the aniline dyes, which it was hoped would be equally specific in their action, and by the aid of which definite organisms could be attacked in the body without affecting the cells of the host.

Salvarsan (page 603) is a drug of this type. Its structure strongly suggests that of an azo dye (note the presence of "chromophore" and "auxochrome" groups).

Two disazo dyes, derived from benzidine in the same manner as is Congo red, are Trypan blue and Trypan red. They have strong trypanocidal action. Two acridine derivatives recently used as antiseptics are Proflavine and Acriflavine:

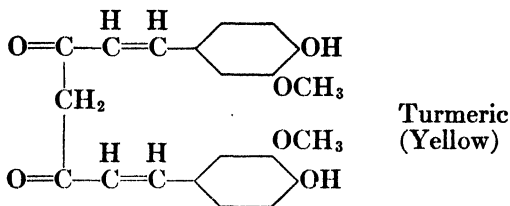


### NATURAL DYES

A number of dye groups have been omitted in the preceding discussion, but enough have been included to illustrate the wide scope of this branch of organic chemistry. In addition to the synthetic dyes we must also consider those of natural origin.

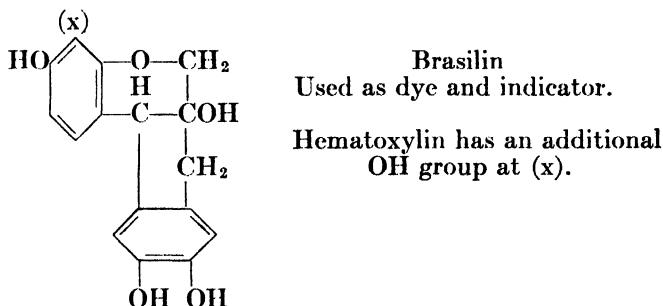
These are obtained from the bark and wood, roots and leaves of various plants and trees. Though by no means so satisfactory as synthetic dyes, various natural dyes still find application. Most of these are mordant dyes, and are found in the plants as glycosides. A number of the yellow dyes are derivatives of the flavone nucleus (page 737). Of those natural dyes now in use a partial list is given below.

*Turmeric*; obtained from the rhizome of *Curcuma longa* (China, East India, etc.):



Turmeric is used in medicine and in analytical work (turmeric paper). It is suitable for dyeing butter, food preparations, for coloring varnish, wallpaper, etc.

*Brazil Wood*. The dyestuff from this source is brasilin (Brazilin):

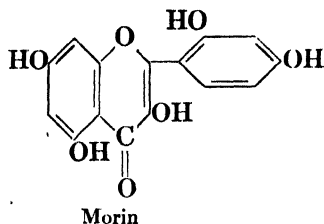
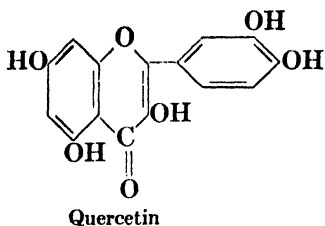


*Logwood*. This contains the coloring matter hematoxylin, similar in structure to brasilin, used for dyeing cloth and leather. Brasilin and hematoxylin are oxidized to produce brasilein and hematein respectively; the structures of these dyes are not given here. *Alizarin* and *indigo*, now made synthetically, were previously obtained from natural sources, alizarin from madder root, indigo from the indigo plant, as already stated.

#### FLOWER PIGMENTS

The pigments of plants, flowers, fruits, are glycosides or glycoside derivatives. Those of yellow hue are derived from flavone or xanthone. Those which are red, violet, or blue are for the most part derived from anthocyanin (page 737).

Among flavone derivatives we find *quercetin*, a constituent of oak bark, tea, onion skin, horse chestnut blossoms. Extract of oak bark is used as a mordant in dyeing leather, also in tanning. *Morin* is found with a polyphenolic compound, Maclurin, in the wood of *chlorophora tinctoria* (Fustic). Both are mordant dyes, giving yellow or olive shades. Fustic wood is used in leather tanning.



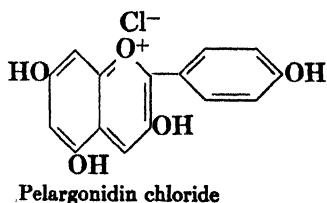
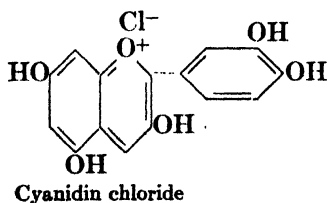
The derivatives of anthocyan nucleus are called anthocyanins. The hydrolysis of these glycosides yields glucose or another sugar, and anthocyanidins, which are colored.

TABLE 46.—U.S. PRODUCTION OF INTERMEDIATES, 1936 AND 1940\*

	Pounds, 1936	Pounds, 1940
H acid.....	3,509,806	4,309,188
1-Naphthylamine-3,6,8-trisulfonic acid.....	4,937,113	4,740,909
R acid.....	638,030	553,200
Nitrobenzene.....	53,669,834	69,105,449
<i>m</i> -Nitroaniline.....	194,250	302,014
Aniline.....	38,495,386	55,719,733
$\alpha$ -Naphthylamine.....	3,479,594	
$\beta$ -Naphthylamine.....	1,007,804	
Phthalic acid and anhydride.....	31,244,378	57,946,415
Chlorotoluene.....	231,985	
Phenol.....	48,723,990	96,155,080
<i>p</i> -Aminophenol.....	660,030	674,643
Benzoylbenzoic acid.....	1,476,104	
Dimethylaniline.....	3,254,468	7,049,741
Dinitrochlorobenzene.....	8,254,081	9,753,665
Metanilic acid.....	406,060	681,181
$\alpha$ -Naphthol.....	1,140,354	558,859
Sulfanilic acid.....	1,678,296	1,941,126

\* Compiled from reports of the U.S. Tariff Commission.

*Cyanidin chloride* is obtained by acid hydrolysis of cyanin, a pigment diglucoside of the cornflower and red rose. It has been synthesized from quercetin by reduction of the keto oxygen (this also involves a change of quinone ring to benzene ring). Otherwise than at this point the molecules are alike. Cyanidin behaves as an indicator, being red in acid and blue in alkaline solution. This property is common to anthocyanidins.



*Pelargonidin chloride*, from flowers of pelargonium species, has a somewhat simpler structure. Delphinidin chloride (pansy, larkspur) has six hydroxyl groups, four as in pelargonidin chloride and two more, each *ortho* to the lone hydroxyl on the phenyl ring.

When the three compounds mentioned are heated with alkali, all give phloroglucinol; in addition we get *p*-hydroxybenzoic acid from pelargonidin,

TABLE 47.—U.S. PRODUCTION OF CERTAIN DYES, 1936 AND 1940\*

	Pounds, 1936	Pounds, 1940
<i>Single Dyes</i>		
Butter yellow.....	25,266	
Bismarck brown.....	103,623	89,466
Tartrazine.....	788,613	573,785
Methyl violet and base.....	927,152	1,321,677
Eosin.....	45,660	52,143
Indigo, synthetic.....	18,039,419	11,133,161
Sulfur black.....	14,585,559	14,633,496
Chrysoidine Y.....		420,740
Sulfur blue.....	1,953,753	2,469,214
Sulfur brown.....	2,388,582	1,806,099
Orange II.....		1,743,652
Direct black EW.....	8,174,156	8,482,298
<i>By Classes</i>		
Azo dyes.....	37,598,624	55,701,277
Pyrazolone.....	1,425,242	1,218,593
Triphenylmethane and related.....	3,685,239	4,663,540
Xanthene.....	714,569†	
Azine.....	2,925,250	
Sulfides and Thiazines.....	20,717,289	21,560,675
Anthraquinone.....	1,864,047	3,421,174
Anthraquinone vat.....	4,894,117†	
Food dyes.....	408,750	
Total classified dyes.....	104,068,929	104,539,151
Total unclassified dyes.....	15,454,217	23,294,429

\* Compiled from Government publications. † 1935.

protocatechuic acid from cyanidin, and gallic acid from delphinidin. Inspection of the formulas will provide a ready explanation for these results.\* It is interesting to note that the variety of colors observed in flowers can be obtained by small changes in a basic formula, and variation in pH.

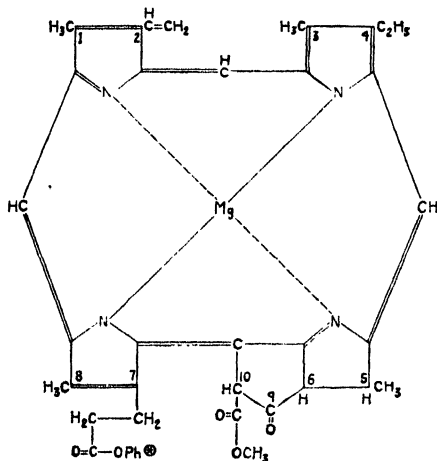
### CHLOROPHYLL

The green coloring matter of plants is usually associated with carotene and xanthophyll, which are carotenoids. Chlorophyll, after extraction, is a

\* In addition to the free hydroxyl compounds shown here we have their mono- and polymethyl ethers, several of which have been found in nature. The opportunity for isomerism afforded in these ethers explains in part the different colors of the compounds. Practically all of the anthocyanidins are to be considered as derivatives of the basic formula represented above.

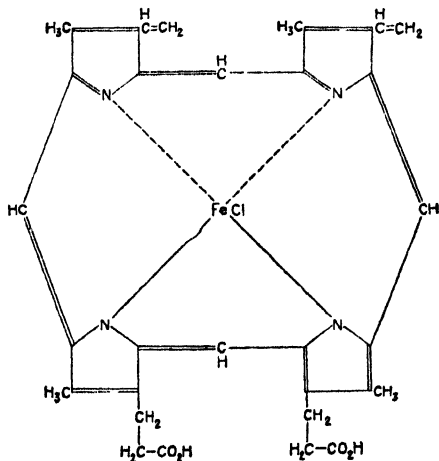


blue- or green-black powder. It has been studied for nearly one hundred years and the accumulated chemical facts would fill a large volume.



The proposed (1936) formula for chlorophyll *b* is like that of *a* but with —CHO at carbon 3 instead of CH<sub>3</sub>.

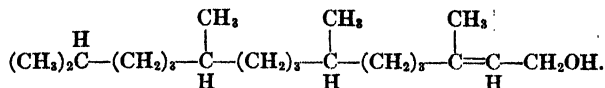
Chlorophyll *a* (Fischer, 1937). A slightly different formula was proposed in 1939 (see *Chem. Abstracts*, 1939, 3387).



Hemin

Two different compounds, chlorophyll *a* and *b*, have been isolated from it by partition between petroleum ether and methyl alcohol. The analysis

\* Ph here stands for the phytol radical. Phytol alcohol (phytol) which is esterified at this point in the molecule, is:



It will be seen that this formula embodies four isoprene units.

of chlorophyll *a* gives the formula:  $(C_{32}H_{30}ON_4Mg)(COOCH_3)(COOC_{20}H_{39}) + \frac{1}{2}H_2O$ , while *b* has the formula  $(C_{32}H_{28}O_2N_4Mg)(COOCH_3)(COOC_{20}H_{39})$ .

There is great similarity between chlorophyll and hemin, constituent of hemoglobin of the blood. Each has a unit of four pyrrole rings and each has an essential metallic atom, magnesium for chlorophyll, and iron for hemoglobin. This will be noted in the formulas for chlorophyll *a* and hemin as shown on p. 704.

Chemical treatment of hemin or of chlorophyll which removes the metallic atom, produces from each the compound aetioporphyrin. This compound preserves the four pyrrole units, grouped as in hemin. Chlorophyll is used to color foods, leather, perfumes, soaps, cosmetics.

TABLE 48.—NATURAL DYES, U.S. PRODUCTION 1925\*

	Pounds
Logwood.....	13,697,000
Fustic.....	3,601,000
Quercitron.....	4,174,000
Brazil wood.....	425,000
Cutch.....	853,000
Total.....	24,627,000

\* Compiled from Government publications.

#### HISTORICAL DATA

- 1771 Picric acid from indigo and  $HNO_3$ , Wolfe.
- 1820 Naphthalene in coal tar, Gardner.
- 1832 Anthracene in coal tar, Dumas.
- 1834 Phenol in coal tar, Mitscherlich.
- Aniline in coal tar, Runge.
- Rosolic acid, Runge.
- Discovery of nitrobenzene, Mitscherlich.
- Aniline with bleaching powder gives blue, Runge.
- 1842 Aniline by reduction of nitrobenzene, Zinin.
- 1845 Benzene in coal tar, Hofmann.
- 1848 Toluene in coal tar, Mansfield.
- 1856 Mauveine, Perkin.
- Magenta, from aniline and ethylene chloride, Natanson.
- 1858 Magenta, from aniline and carbon tetrachloride, Hofmann.
- Diazo reaction, Griess.
- 1859 Safranine T.
- Magenta from aniline and  $SnCl_4$ , Verguin.
- 1860 Aniline blue, also Magenta by oxidation of aniline with arsenic acid, Girard and deLaire.
- 1861 Methyl violet, Lauth.
- Phosphine, Nicholson.
- 1862 Sulfonation reaction, Nicholson.
- 1863 Violets, Hofmann.
- Indulines, Dale and Caro.
- Bismarck brown, Martius.
- 1865 Benzene structure, Kekulé.
- 1867 Martius yellow, Martius and Caro.
- 1868 Alizarin, Graebe and Liebermann.

- 1874 Eosin, Baeyer (Caro).
- 1875 Erythrosine.  
Chrysoidine, Caro.
- 1876 Orange II, Poirrier.  
Witt chromophore theory.
- 1878 Malachite green.
- 1879 Naphthol yellow S, Caro.
- 1880 Para red, Holliday Co.  
Indigo, Baeyer.
- 1883 Auramine, Caro and Kern.  
Crystal violet, Caro and Kern.
- 1884 Congo red, Büttiger.  
Tartrazine.
- 1887 Primuline, Green. Ingrain dyes, Green.  
Rhodamine B.
- 1888 Use of  $\text{H}_2\text{SO}_4$  in making alizarin, Bohn.  
Oxazines, Rosindulines, Fischer and Hepp.
- 1893 Vidal black, (Sulfur dye).
- 1897 Synthetic indigo, Badische Co.
- 1899 Use of formaldehyde; Pyronines, Acridines, Höchst Co.
- 1901 Indanthrene blue, Bohn.
- 1906 Thioindigo red, Friedlander.
- 1912 Naphthol AS red.

See also the historical table in the Appendix, p. 800.

### REVIEW QUESTIONS

1. Give a working definition of the term "dye compound."
2. Define: (a) Fugitive dye; (b) Lake; (c) Polygenetic dye; (d) Mordant; (e) Indicator.
3. Upon what structural arrangement does the color of an organic compound depend? What is an auxochrome?
4. Show by equations the synthesis of an azo compound from aniline and phenol. Name the compound.
5. Write equations for the synthesis of methyl orange. What is an explanation of the indicator action of this compound?
6. What is meant by the terms leuco base, and color base? Illustrate by the use of derivatives of triphenylmethane.
7. Give equations for the synthesis of pararosaniline. How is the action of acids, etc., (formation of a dye) explained?
8. Give equations for the formation of phenolphthalein. Show and discuss its reaction with NaOH solution.
9. Write equations for the synthesis of: (a) Indigo; (b) Direct black EW; (c) Hansa yellow G; (d) Crystal violet; (e) Fluoran; (f) Alizarin.
10. What groupings cause color in an organic compound? Are colored compounds of necessity dyes? Why?
11. What is a direct dye? Give example. Also give example of a mordant dye.
12. Give synthesis of one member of each of the following dye groups: (a) Triphenylmethane; (b) Azo; (c) Nitro; (d) Phthalein.
13. Show by a series of equations the synthesis of tartrazine.
14. Suggest methods for making phenol red and bromphenol blue.
15. Enumerate various points of difference between a dye structure like that of indanthrene violet R and one like congo red.
16. Observe the arrangement of double and single bonds in chlorophyll *a*. Do you note any peculiarity?

17. After a survey of the dye formulas of this chapter, which chromophores seem most important to you?
18. What facts can you cite which support the chemical theory of dyeing?
19. Write equations for the synthesis of orange II.
20. Name compounds used in medicine which are dyes or are derived from dyes. Give uses for each.
21. Cite a number of reasons why aliphatic compounds cannot compete with aromatics for the production of dyes.
22. Show the synthesis of rhodamine B, starting with naphthalene and benzene.
23. Can you account in any way for the large increase in production of phthalic anhydride and phenol (shown by the table, page 702)?
24. Phthalimide and isatin are isomeric compounds. Refer to a handbook or to museum samples to learn the color of each and discuss your findings.
25. With the aid of a handbook make a chart listing the compounds mentioned in this chapter which are used as indicators. For each compound show name, graphic formula, range of *pH* governing the change of color, also the colors shown by each compound in its various forms.
26. What factors cause ingrain and vat dyes to show greater fastness than direct dyes?
27. What compounds would be formed upon the vigorous reduction of: (a) Chrysoidine; (b) Para red; (c) Orange II?
28. An organic dye (A) has the formula  $C_{12}H_{11}N_3$ . Strong reduction gives two compounds, (B) and (C). (B) is aniline. (C) is capable of diazotization; its oxidation yields quinone. Its formula is  $C_6H_8N_2$ . With these facts attempt to prove the structure of (A).
29. A colored organic compound (A) contains 73.93% C, 6.16% H, and 19.90% N. Its reduction with tin and hydrochloric acid gives compounds (B) and (C). (B) gives an alkali-soluble compound by reaction with benzenesulfonyl chloride. (B) was diazotized and the resulting solution then treated with cuprous bromide and hydrobromic acid. The new compound (D) produced in this reaction had a melting point of 28.5°C. It contained 49.12% C, 4.10% H, and 46.8% Br. (C) contains 66.65% C, 7.41% H, and 25.93% N. It is capable of diazotization. If it were diazotized with one equivalent of nitrous acid and the solution then heated, the compound (E) of m.p., 184°C. would be formed. (E) may be produced by heating  $\beta$ -phenylhydroxylamine with acid. What is the structure of (A) and of the compounds (B) and (C)?

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## CHAPTER XXXVII

### PROTEINS

Like the fats and carbohydrates, proteins are substances synthesized by living cells. They form an essential part of the diet and constitute the chief part of the solid matter of animal tissues. It would be difficult to give a hard and fast definition of the term protein in chemical language since, due to the instability and non-crystalline nature of these substances, they have so far eluded the chemist's attempts at their isolation as individual compounds with fixed characteristics. In such a situation there is also some uncertainty as to their chemical constitution. The utmost we can attempt here is to briefly summarize what is now known about these compounds.

Proteins contain carbon, hydrogen, oxygen, nitrogen, sulfur, phosphorus, sometimes iron and other elements. The proportions of these elements vary in the several types of proteins, but average values generally fall within the limits shown here:

Carbon.....	50-55 %
Hydrogen.....	6.5-7.3
Oxygen.....	20-24
Nitrogen.....	15-18
Sulfur.....	0.4-2.5
Phosphorus.....	0.1-1.0

Since the percentage of nitrogen in proteins is observed to lie very close to 16%, analysts have made use of this in estimating the amount of protein in a given sample. The amount of nitrogen is found by Kjeldahl analysis and multiplied by the factor 6.25 (this is  $100/16$ ), to give the percentage of protein in animal and plant substances.

Considering that proteins are derived from substances of widely different physical properties, such as skin, hair, muscles, horn, silk, egg-white, etc., the narrow range of percentage composition as shown above is remarkable.

The **molecular weights** of proteins have been determined in several different ways which give fairly concordant results. The following *chemical method* has been used to estimate the molecular weight of certain proteins which contain small amounts of one element. Hemoglobin for instance contains a very small percentage of iron (0.335%). Now if we assume that the molecule of hemoglobin has one atom of iron (it could not well have less), calculation from the percentage composition of this element leads to a molecular weight value of 16,669 for hemoglobin. If we calculate from the

percentage of sulfur in hemoglobin (0.390%) we obtain the figure 16,446. The *osmotic pressure method* gave a value of 34,000 for the molecular weight of egg albumin, 69,000 for serum albumin. Such calculations make it evident that the proteins are larger molecules than any we have so far studied. There is no doubt that they are more complex in their structural make-up than any other class of compounds.

Still higher figures for molecular weights are obtained by the *use of the ultracentrifuge* (Svedberg). A protein solution is centrifuged at high speed, and the molecular weight of the particles determined by the velocity of sedimentation observed. The weights obtained by this method appear to be multiples of 35,100, which is about twice the value obtained (for some proteins) by the chemical method. Some of Svedberg's values are:

Egg albumin.....	43,800
Serum albumin.....	67,500
Lactalbumin.....	17,300
Hemoglobin.....	70,200
Hemocyanin.....	842,000

The fact that the molecular weight figures are divisible by 35,100 may be accidental, or may be an indication that a repeating unit of this size exists in native proteins (see page 730). It is fairly evident that the original assumption (one Fe atom in hemoglobin) is incorrect.

### PROTEIN CHARACTERISTICS

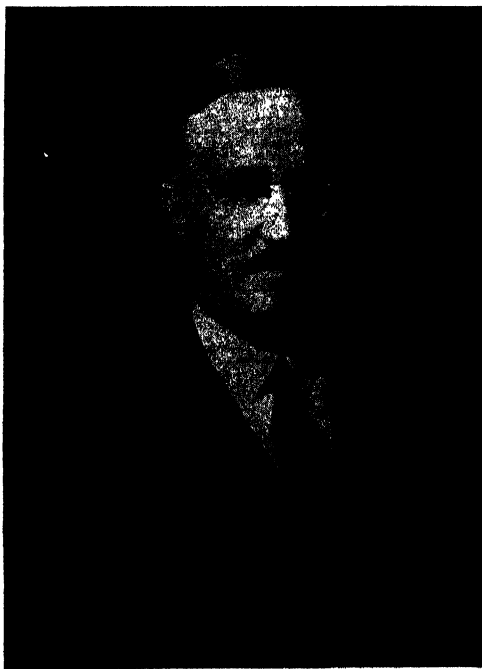
The majority of proteins are amorphous colorless compounds, which do not have definite melting points or definite boiling points. They are insoluble in organic liquids. Those which dissolve in water give colloidal solutions. Proteins are precipitated or "salted out" from their solutions by the addition of inorganic salts ( $\text{Na}_2\text{SO}_4$ ,  $\text{NaCl}$ ). A number of other substances, including heavy metal salts, phosphotungstic acid, tannic acid, and other of the "alkaloidal reagents" (page 658) induce precipitation. Certain of the color and precipitation reactions used to test for proteins are listed at a later point in the chapter.

*Denaturation* of proteins refers to a lessened water solubility caused by the action of heat, high pressure, alcohol, alkali, acid, and certain other reagents. A denatured protein is insoluble in water at its isoelectric point. It may be dissolved by the addition of acid or base, and in some cases the denaturation may be reversed. Apparently denaturation involves chemical changes in the protein molecule. Theories regarding these changes will be found in advanced texts. Following denaturation the protein precipitates; the total effect, denaturation and precipitation, is known as coagulation.

### CLASSIFICATION OF PROTEINS

As the usual criteria for identification of an organic compound such as melting point, boiling point, molecular weight, crystal form, cannot be

**THOMAS MIDGLEY, JR.** (American, 1889–1944.) Midgley is known for his studies of the knocking characteristics of various types of fuels and for the development of chemical antiknock agents. We owe the use of tetraethyllead to his research, as well as the technology of its manufacture. He has had a prominent part in work dealing with the chemistry of rubber. Midgley developed the organic chlorofluoride compounds, widely used as non-inflammable, non-toxic refrigerants. See *Ind. Eng. Chem.*, **31**, 504 (1939); **36**, 1073 (1944); also News Edition, **19**, 1021 (1941)



**ROGER ADAMS.** (American, 1889– .) Work with chaulmoogric acid, stereochemistry of biphenyl compounds, deuterium compounds, anesthetics (butyn, butesin), dyes, catalytic hydrogenation, gossypol, alkaloids. Co-author of the well known laboratory text for organic chemistry, and editor of *Organic Reactions*. Now head of the Chemistry Department in the University of Illinois.



applied in the case of the proteins, the basis for their classification rests mainly upon their "solubility" in various media. This is a purely empirical classification but nevertheless useful. It is not claimed that the materials obtained by the use of the reagents listed here are single molecular species. The following table, which is that adopted by the American Society of Biological Chemists, shows the manner in which proteins are grouped and classified, and has been amplified to give the source of the more common proteins.

**Simple Proteins.** These when broken down into simpler units yield only *alpha* amino acids or their derivatives. We have the following sub-groups:

A. *Albumins*. Coagulated by heat, soluble in water and in dilute salt solutions. *Egg albumin*, *serum albumin* of blood, *lactalbumin* of milk.

B. *Globulins*. Found in seeds and in animal blood. Coagulated by heat, insoluble in water, soluble in dilute neutral solutions of the salts of strong acids and bases ( $\text{NaCl}$ ,  $\text{MgSO}_4$ ). *Serum globulin* of blood, *edestin* in hemp seed.

C. *Glutelins*. Found in seeds. Insoluble in water or dilute salt solutions. Soluble in dilute acid or alkali. *Glutenin* in wheat.

D. *Prolamines*. Found in cereal grains. Insoluble in water, soluble in 80% alcohol. *Gliadin* from wheat. *Hordein* from barley, *zein* from corn.

E. *Albuminoids*. Found in connective tissue, hair, wool, horn, nails, etc. Insoluble in water, salt solutions, dilute acid, or alkali. *Elastin* in ligaments, arterial walls. *Keratin* in hair. *Collagen* in connective tissue.

F. *Histones*. Not coagulated by heat, soluble in water, or in dilute acid; they are basic and insoluble in dilute ammonium hydroxide. Their hydrolysis gives a number of amino acids, especially diamino acids. *Histone* from thymus gland.

G. *Protamines*. Not coagulated by heat, soluble in ammonium hydroxide and in water. They are basic and form stable salts with strong acids. Decomposition gives notable amounts of diamino acids. *Sturine* in sturgeon sperm. *Salmine* in salmon sperm.

**Conjugated Proteins.** The decomposition of these compounds shows them to be made up of simple proteins and other groups, non-protein in character.

A. *Chromoproteins (Hemoglobins)*. The simple protein in these compounds is united with a colored group. *Hemoglobin* of red blood corpuscles.

B. *Glycoproteins*. As suggested by the name the additional group is carbohydrate in nature. *Mucin* in saliva.

C. *Phosphoproteins*. Found in milk and egg-yolk. Phosphorus forms a part of the molecule. *Casein*, milk. *Vitellin*, egg-yolk.

D. *Nucleoproteins*. Nucleic acid is the additional group. *Nuclein*.

E. *Lecithoproteins*. Additional group is lecithin.

F. *Lipoproteins*. Additional group is one of the higher fatty acids.

**Derived Proteins.** This group contains those substances produced from natural proteins by the action of reagents, and also proteins of synthetic origin.

*A. Primary Protein Derivatives.*

(a) Proteans. Insoluble in water. The first products resulting from action of acids, enzymes, or water. *Edestan* from edestin.

(b) Metaproteins. These result from the prolonged action of hydrolytic agents upon proteins. They are soluble in weak acid or alkali, but are insoluble in neutral solutions. *Acid albuminate* (Acid metaprotein). *Alkali albuminate* (Alkali metaprotein).

(c) Coagulated proteins. Insoluble products resulting from the action of heat or strong alcohol upon proteins.

*B. Secondary Protein Derivatives.*

(a) Proteoses. These are soluble in water and may not be coagulated by heat. They are precipitated from water solutions by saturation with ammonium sulfate.

(b) Peptones. These products are soluble in water, but are not coagulated by heat nor precipitated by saturation with ammonium sulfate. They give the biuret reaction (page 723).

(c) Peptides. These substances are of such simplicity that their structures may be determined. They are made up (as will be later described) of several molecules of amino acid, and have somewhat the structure of amides.

## CHEMISTRY OF PROTEINS

Proteins show considerable differences in their chemical action; most proteins, however, exhibit the character of amphoteric compounds, forming salts with either bases or acids. This point will be referred to later. The most characteristic reaction of the proteins is their hydrolysis, which may be accomplished by the use of acid or alkaline solutions, or by means of enzymes.

As hydrolysis proceeds there is evidence that the original molecules are being broken down into simpler substances (proteoses). Thus salts which precipitate the original protein may fail to cause a precipitate after a short period of hydrolysis, or a protein which could be coagulated by heat might lose this property. Further hydrolysis yields still more simple substances (peptones). The complete hydrolysis of a simple protein gives a mixture of amino acids. Of these twenty-three have been definitely certified. They are  $\alpha$ -amino acids of a number of different chemical types. The relative amounts of the different amino acids vary widely in the different proteins, and no protein is known which yields but one amino acid upon hydrolysis.

Certain proteins are entirely lacking in several of the amino acids; others contain very high percentages of a few acids. The table, p. 714, which is obtained from a number of sources, is instructive in this connection. The

analysis of a protein does not always give a 100% yield of products, due to the difficulties inherent in the work; for the same reason the results obtained by different investigators are not expected to check with exactness.

TABLE 49.—AMINO ACIDS OF PROTEINS

	Lactalbumin	Casein	Gelatin	Silk fibroin	Salmine	Wheat gliadin	Wheat glutenin	Zein
Glycine.....	0.4	.....	25.5	40.5	.....	.....	0.9	.....
Alanine.....	2.5	1.5	8.7	25.0	.....	2.0	4.7	9.8
Valine.....	3.3	7.2	.....	.....	4.3	3.4	0.2	1.9
Leucine.....	14.0	9.4	7.1	2.5	.....	6.6	6.0	25.0
Aspartic acid.....	9.3	4.1	3.4	.....	.....	0.6	0.9	1.8
Glutamic acid.....	12.9	21.6	5.8	.....	.....	43.7	23.4	31.3
Serine.....	.....	5.5	3.4	1.6	7.8	0.2	0.7	2.6
Hydroxyglutamic acid.....	10.0	10.5	.....	.....	.....	.....	.....	2.5
Phenylalanine.....	1.2	3.2	1.4	1.5	.....	2.4	2.0	7.6
Tyrosine.....	1.9	6.5	0.01	10.5	.....	3.2	4.3	3.6
Tryptophan.....	2.7	1.7	.....	.....	.....	1.0	*	.....
Cystine.....	4.0	0.3	.....	.....	.....	2.5	0.02	1.0
Methionine.....	2.3	1.4	1.0	.....	.....	.....	.....	2.9
Lysine.....	8.4	2.6	5.9	0.3	.....	0.2	1.9	.....
Arginine.....	3.2	3.8	8.2	0.9	87.4	3.2	4.7	1.8
Histidine.....	1.5	7.5	0.9	0.1	.....	2.0	1.8	0.8
Proline.....	4.0	8.0	19.5	1.0	11.0	13.2	4.2	9.0
Hydroxyproline.....	.....	0.3	14.1	.....	.....	.....	.....	.....
Ammonia.....	1.3	1.6	0.4	.....	.....	5.2	4.0	3.6
Total.....	82.9	96.7	105.31	83.9	110.5	89.4	59.72	105.2

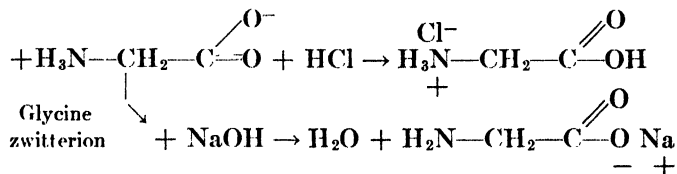
### PROPERTIES OF PROTEIN AMINO ACIDS

These are colorless crystalline compounds, water-soluble (except cystine and tyrosine). They are in general soluble in dilute alcohol, not in absolute alcohol or in ether or common organic solvents. The amino acids have no true melting points but decompose when heated to 200–350°C. These properties resemble those of inorganic salts (see later discussion, page 715).

The amino acids are acid, neutral, or basic in reaction, as they possess respectively an overplus of carboxyl groups, an equality of carboxyl and amino groups, or an overplus of amino groups. All are optically active save glycine, for which activity is impossible. Either the *d*- or the *l*-form of a given acid is found in proteins, but not both. A number of the acids, for example, glycine, alanine, serine, norleucine, are sweet in taste.

**Zwitterions.** The amino acids are amphoteric, i.e., can act either as acids by virtue of the carboxyl group or as bases by virtue of the amino group. In solution the molecules may have both positive and negative

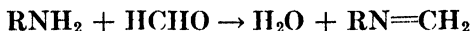
charges, due to the chemical behavior of these opposed groups. This type of ion is known as a zwitterion. At some definite *pH* the acid and basic ionization would be of equal extent. This is known as the "isoelectric point." Taking glycine for an example we can show the reaction of the zwitterion with acid and base as follows:



The individual molecules of a solid amino acid must be supposed to exist as an internal salt or zwitterion (see page 245). This formulation explains the anomalous points already mentioned (high melting point, insolubility in organic solvents), which are properties of salts and not of organic acids. The same type of structure was proposed for sulfanilic acid (page 469) which has similar properties.

#### CHEMISTRY OF AMINO ACIDS

- (1) The amino group reacts in the expected way with acid chlorides, anhydrides (see pages 189, 193, 274, 310).
- (2) Nitrous acid reacts with amino group to give nitrogen and hydroxyl group. A measurement of the evolved nitrogen is used to estimate amino group (Van Slyke test).
- (3) Formaldehyde reacts by condensation:



The free amino groups are in this way removed from competition and the carboxyl groups may be estimated by titration (the "formol" titration).\*

- (4) The carboxyl group forms salts in the usual way, and esters. The formation of acid chlorides, and other reactions of amino acids will be given at the appropriate places.

#### AMINO ACIDS OF PROTEINS

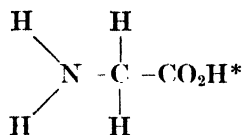
The list below shows most of the amino acids which have been identified.† The italic letters give the actual optical rotations of the natural amino acids. All of the acids have the same spatial configuration at the *alpha* carbon atom and belong to the *levo* series (see page 336).

\* This is a simplified version; actually the reaction is more complex. The symbol R represents all of the amino acid save the  $\text{NH}_2$  group.

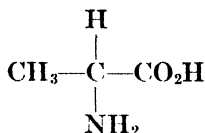
† The figures in parentheses give the dates when the amino acids were first isolated from proteins, when first synthesized in the laboratory, and the melting points or decomposition temperatures, respectively.

**Monocarboxylic Acids with One Amino Group.**

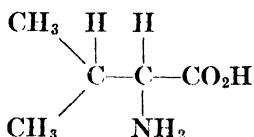
Glycine, glycoll, aminoacetic acid (1820, 1858, 232–6° dec.):



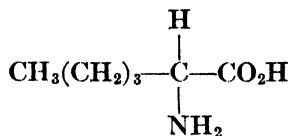
*d*-Alanine,  $\alpha$ -aminopropionic acid (1888, 1850, 295° dec.):



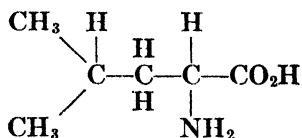
*d*-Valine,  $\alpha$ -isopropyl- $\alpha$ -aminoacetic acid (1901, 1880, 315° dec.):



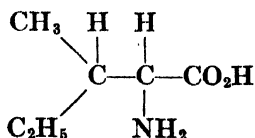
*d*-Norleucine,  $\alpha$ -amino-*n*-caproic acid (1901, 1870, 301° dec.):



*l*-Leucine,  $\beta$ -isopropyl- $\alpha$ -aminopropionic acid (1820, 1855, 293–5° dec.):



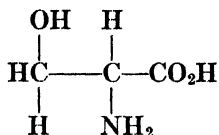
*d*-Isoleucine,  $\alpha$ -amino- $\beta$ -ethyl- $\beta$ -methylpropionic acid (1904, 1905, 275°):



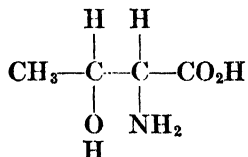
\* This was the first amino acid obtained by hydrolysis of a protein. (Braconnot, 1820.)

**Hydroxy Monamino Acids.**

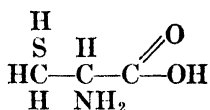
*l*-Serine,  $\beta$ -hydroxy- $\alpha$ -aminopropionic acid (1865, 1902, 228° dec.):



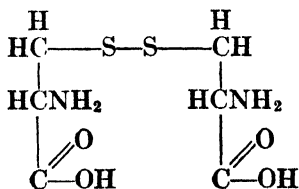
*l*-Threonine,  $\alpha$ -amino- $\beta$ -hydroxybutyric acid (1926, 1936, 256° dec.):

**Sulfur-containing Acids.**

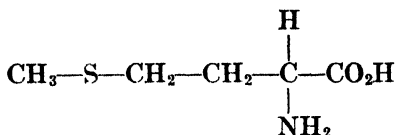
*l*-Cysteine,  $\beta$ -thiol- $\alpha$ -aminopropionic acid:



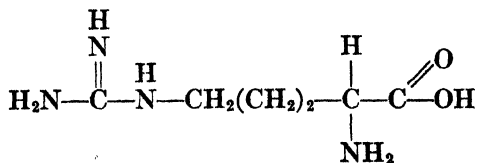
The disulfide corresponding to Cysteine is *l*-Cystine (1899, 1903, 258–61° dec.):



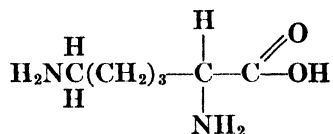
*l*-Methionine,  $\gamma$ -methylthiol- $\alpha$ -aminobutyric acid (1922, 1928, 283° dec.):

**Monocarboxylic Acids with Two Amino Groups.**

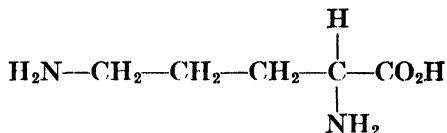
*d*-Arginine,  $\alpha$ -amino- $\delta$ -guanidovaleric acid (1895, 1910, 238° dec.):



*d*-Lysine,  $\alpha$ ,  $\epsilon$ -diaminocaproic acid (1889, 1902, 224° dec.):

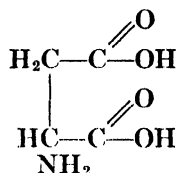


*d*-Ornithine,  $\alpha$ ,  $\delta$ -diaminovaleric acid:\*

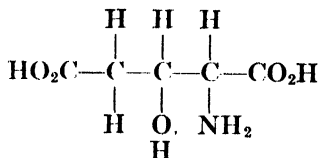


### Dicarboxylic Acids with One Amino Group.

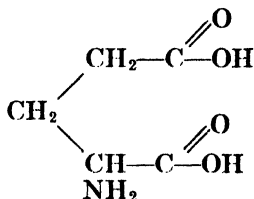
*l*-Aspartic acid,  $\alpha$ -aminosuccinic acid (1868, 1887, 271° dec.):



*d*-Glutamic acid,  $\alpha$ -aminoglutaric acid (1866, 1890, 247–9° dec.):

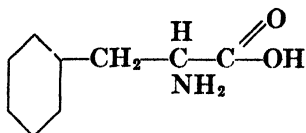


*d*-Hydroxyglutamic acid,  $\beta$ -hydroxy- $\alpha$ -aminoglutaric acid (1919, 1919, 135°):



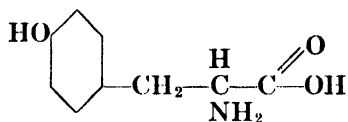
### Aromatic Homocyclic Derivatives.

*l*-Phenylalanine,  $\beta$ -phenyl- $\alpha$ -aminopropionic acid (1881, 1882, 283° dec.):

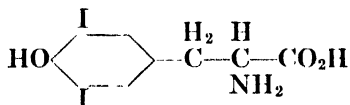


\* Ornithine is formed in the liver by the action of the enzyme arginase upon arginine.

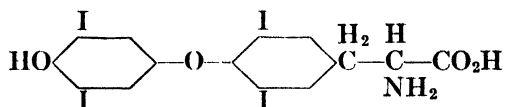
*l*-Tyrosine,  $\beta$ -[*p*-hydroxyphenyl]- $\alpha$ -aminopropionic acid (1849, 1882,  $>290^\circ$  dec.):



*l*-Iodogorgoic acid, 3,5-diiodotyrosine (1896, 1905):

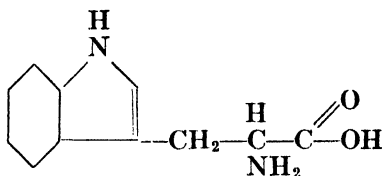


*l*-Thyroxine (1915, 1927,  $232^\circ$  dec.):

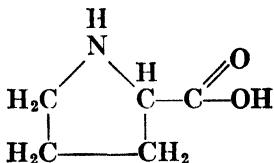


### Heterocyclic Derivatives.

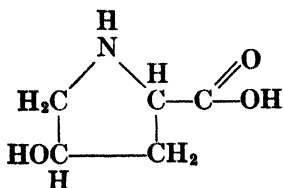
*l*-Tryptophan,  $\alpha$ -amino- $\beta$ -3-indolepropionic acid (1901, 1907,  $289^\circ$ ):



*l*-Proline, pyrrolidine-2-carboxylic acid (1901, 1900,  $220^\circ$ - $222^\circ$  dec.):

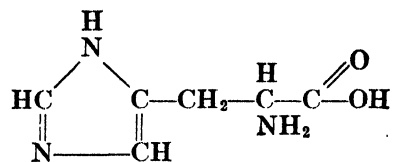


*l*-Hydroxyproline (1902, 1905):





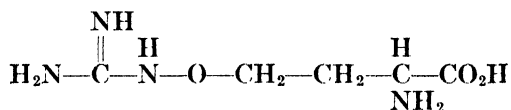
*l*-Histidine,\*  $\alpha$ -amino- $\beta$ -imidazolepropionic acid (1896, 1911, 287-8°):



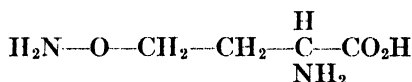
#### Additional Acids.

The following amino acids have been reported as protein constituents; further confirmation is desirable in these cases.

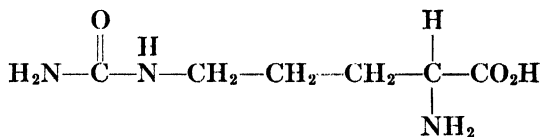
Canavanine (from jack beans),  $\gamma$ -guanidino-oxy(guanidoxy)- $\alpha$ -aminobutyric acid:



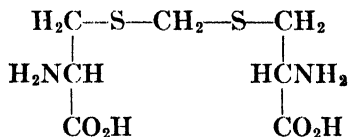
Canaline (from canavanine),  $\gamma$ -aminoöxy- $\alpha$ -aminobutyric acid:



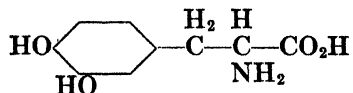
Citrulline,  $\delta$ -carbamido- $\alpha$ -aminovaleric acid:



Djenkolic acid, cysteine thioacetal of formaldehyde:

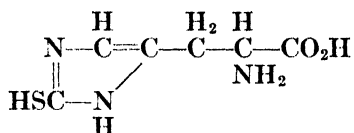


*l*-Dihydroxyphenylalanine (from *Vicia faba*),  $\beta$ [3,4-dihydroxyphenyl]- $\alpha$ -aminopropionic acid:



\* This acid is usually placed together with lysine and arginine as it is basic.

Thiolhistidine,  $\beta$ -[2-thiolimidazole]- $\alpha$ -aminopropionic acid:



**Essential and Indispensable Amino Acids.** Experiments with laboratory animals have shown the wisdom of providing in the diet those amino acids which are necessary for protein synthesis (essential acids). However certain of these amino acids may also be synthesized in the body. Those which cannot be synthesized in the body are known as indispensable amino acids.

Indispensable acids are: Lysine, tryptophan, valine, histidine, leucine, isoleucine, phenylalanine, threonine, methionine.

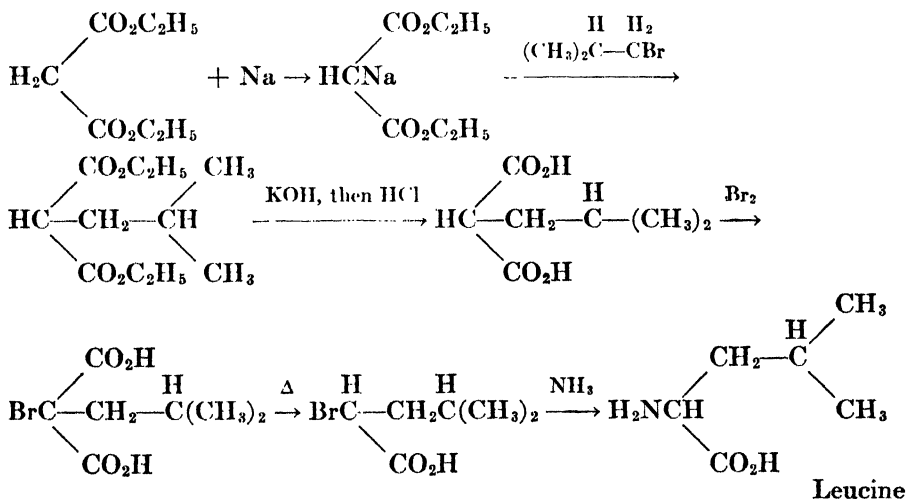
Possibly one or two other acids will later be added to this list. Arginine, while it may be synthesized *in vivo*, is not made in sufficient amount. In tests with animals it was necessary to supply some in the diet.

#### SYNTHESES OF AMINO ACIDS

(1) *From halogen acid and ammonia* (see page 244).

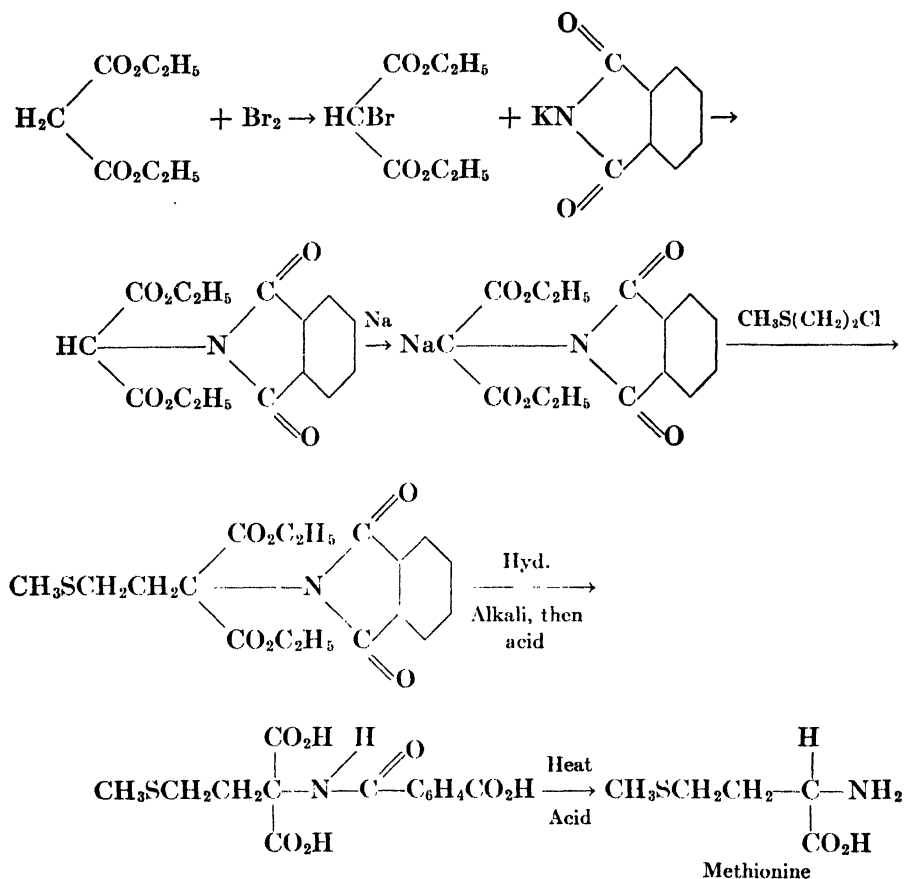
(2) *By the Strecker reaction* (page 244).

(3) *By the use of malonic ester.* The reactions indicated below in condensed form have all been studied before (page 257).



Isoleucine, proline, and phenylalanine may be made by this method.

(4) *By use of phthalimide.* One of several applications of phthalimide to amino acid synthesis is given in the form of a continuous equation. All of the reactions are already familiar from previous work.



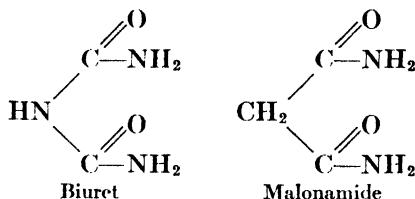
Several other methods both of general and special application will be found in the larger biochemistry texts.

**Biosynthesis of Proteins.** Man and higher animals depend wholly upon plants for the amino acids. Proteins are formed in the leaves from nitrates and nitrites. The precise way in which this is done is unknown, though there is no lack of theory concerning the process. Attempts have been made to duplicate the natural process by the illumination of aqueous salt solutions. See References 13 and 14, page 733.

#### COLOR REACTIONS OF THE PROTEINS

When subjected to the action of certain reagents, proteins yield colored products by which their presence may be detected. In certain instances the presence or absence of definite amino acids is shown by these tests; for this reason their discussion was postponed until the various amino acids had been enumerated.

(1) **Biuret Reaction.** In applying the biuret test the protein solution is made alkaline with sodium hydroxide, and a drop or two of dilute copper sulfate solution is added. The appearance of a red-violet or blue-violet color in the solution confirms the test. This test is given by compounds which contain acid amide groups in close proximity:



and hence is common not only to proteins, but also to substances like biuret (from which the reaction gets its name), and malonamide.

(2) **Millon Reaction.** Millon's reagent is made by dissolving mercury in concentrated nitric acid, later diluting with water. It contains mercuric nitrate and nitrite. The test consists in the development of a red color or a red precipitate, when a protein is allowed to stand with the reagent or the mixture is heated. The reaction depends upon the presence of a hydroxy-phenyl group, and is therefore positive for tyrosine. Non-protein compounds like phenol, salicylic acid, etc., also give the test.

(3) **Xanthoproteic Reaction.** The majority of proteins when treated with concentrated nitric acid give a yellow color or a yellow precipitate. Treatment with a base changes the color to orange. This test depends upon the presence of benzene nuclei in the protein (formation of nitro- and dinitrobenzene derivatives), and hence is specific for tyrosine and tryptophan.\* This reaction and the Millon reaction are more delicate than the biuret test.

(4) **Tryptophan Reactions.**

(a) **Adamkiewicz reaction.** If a protein which contains tryptophan is treated with glacial acetic acid, and a few cc. of concentrated sulfuric acid are added, a violet ring appears at the junction of the acid and water layers. The test was shown to be due to the presence of glyoxylic acid, HCOCOOH, in the acetic acid.

(b) In the Hopkins-Cole test the glacial acetic acid is substituted by glyoxylic acid (made by the reduction of oxalic acid with magnesium powder), the manner of applying the test remaining the same.

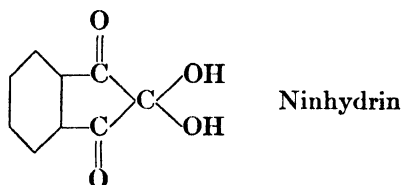
If milk containing formaldehyde is heated with hydrochloric acid and a trace of ferric ion, the tryptophan of the casein yields a violet coloration. This test is very delicate in the presence of the formaldehyde.

(5) **Molisch Reaction.** Those proteins which contain a carbohydrate group will respond to the Molisch test (see page 354).

\* Phenylalanine does not nitrate easily.

(6) **Sulfur Test.** Proteins which contain either cysteine or cystine are decomposed when heated with sodium hydroxide solution, yielding sodium sulfide. The addition of a soluble lead salt gives a precipitate of lead sulfide.

(7) **Ninhydrin Reaction.** *Alpha* amino acids give with triketohydrindene hydrate (ninhydrin) a blue to violet-red color. This is a very delicate test both for the proteins and amino acids.



### PRECIPITATION REACTIONS OF PROTEINS

As proteins contain groups capable of salt formation with both acids and bases, it is natural that they should be precipitated from their solutions by both acidic and basic reagents. The following acids are among those which yield insoluble precipitates with proteins: picric, tannic, phosphomolybdic, phosphotungstic, chromic, metaphosphoric, ferrocyanic. The very delicate Heller test for albumin in urine depends on its precipitation in a "ring" upon layering with nitric acid.

Basic substances causing precipitation include natural bases such as strychnine, quinine, and other alkaloids, and the ions of copper, lead, mercury, platinum, gold, etc. Saturation with ammonium sulfate precipitates all proteins save the peptones. Similarly sodium chloride in acid solution precipitates all save peptones.

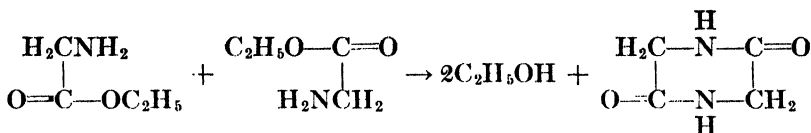
Many acid and basic dyes cause the precipitation of proteins.

### STRUCTURE OF THE PROTEINS; SYNTHESIS OF PEPTIDES

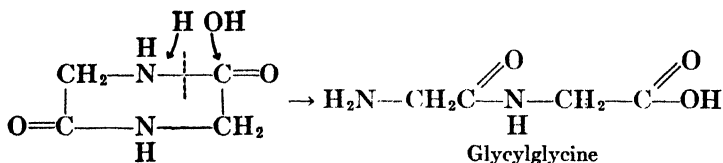
Hydrolysis of simple proteins by acid or alkaline solutions, superheated steam, or by the use of enzymes, always breaks them down into the amino acids. It is therefore fair to assume that these acids already exist in the protein molecule and are not formed during the degradation, since in such an event the different methods of attack should yield different products.\* One may therefore speculate on the way in which the amino acids are joined in the proteins, and by experimentation seek to verify the speculation.

It was shown in the section on amino acids (page 245) that these substances may form ring compounds by loss of water, when treated with dehydrating agents. It is more practical, however, to employ the ester in this reaction, in which case alcohol is lost in the ring formation:

\* This viewpoint is not accepted by some chemists, who assert that proteins are built up of more complex units than the amino acids.



Other amino acids react similarly, forming ring compounds belonging to the group called diketopiperazines. These ring compounds may be partially hydrolyzed if treated with dilute acids, in this way forming a product in which two molecules of amino acid are joined:



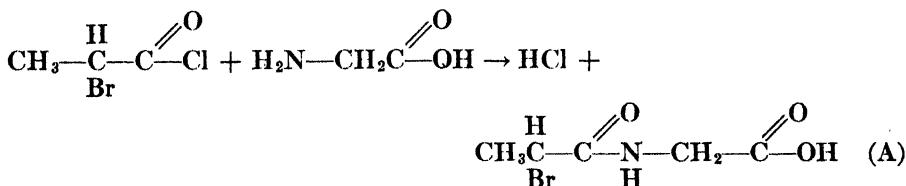
Such a compound is termed a dipeptide; three molecules so joined form a tripeptide; in general a group of amino acids joined in this common relation is called a polypeptide. As indicated by the table on page 713, polypeptides are found among the decomposition products of natural proteins. It seems highly probable that the simple proteins are polypeptides; however the method of synthesis shown above reaches its limit with the dipeptides, and will not serve for more complicated molecules. Another procedure based upon familiar reactions of the alkyl and acyl halides has been used with good effect to synthesize polypeptides.

(1) It will be recalled that chlorine and bromine react with fatty acids to yield  $\alpha$ -halogen acids (page 234).

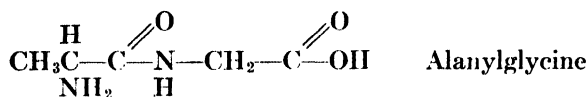
(2) Also it has been shown that phosphorus chloride in reaction with aliphatic acids yields acid chlorides (see page 187).

(3) Again, acid chlorides react with ammonia or the amino group to form amides (see page 189).

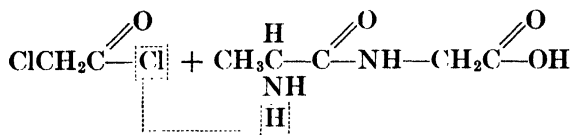
Taking advantage of these facts, a dipeptide may be formed by the reaction of a bromo acid chloride with any amino acid or, better, with its ester



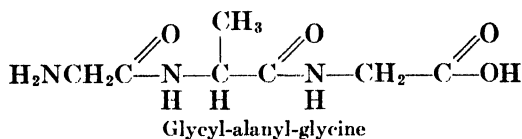
By the action of ammonia a primary amino group is introduced, and the synthesis of a dipeptide is completed:



Now the primary  $\text{NH}_2$  group of this dipeptide is also subject to attack by acid chlorides in the usual way:



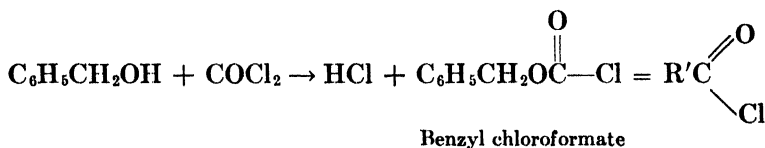
and by the further action of ammonia (4) the synthesis of a tripeptide may be carried out:



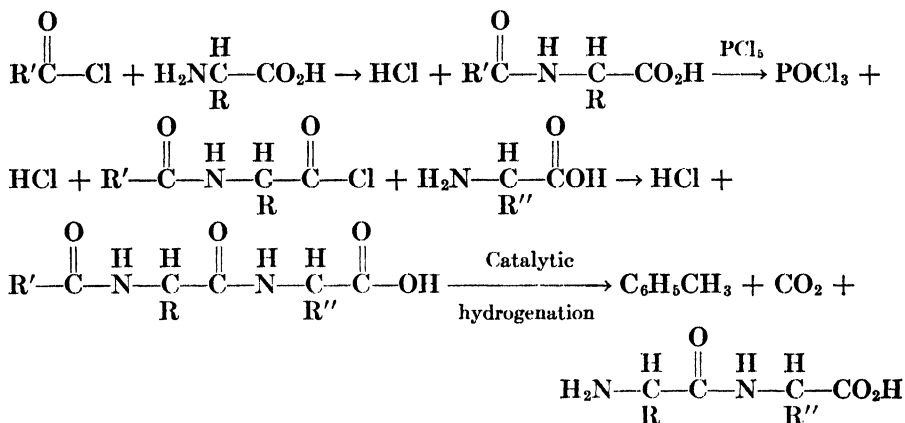
It will be noted that these peptides are named like substitution products of simple amino acids; i.e., the name glycyl-glycine intimates that the glycyl group is substituted for one hydrogen atom of glycine ( $\alpha$ -aminoacetic acid).

The synthetic method just given has the disadvantage that it lengthens the molecule only at one end. It would be possible to operate at the other end of the molecule if an acid chloride could be made. For some time it was found impossible to make acid chlorides of amino acids, however this was finally accomplished in several ways.

The **Bergmann method** involves preliminary reaction with the half ester-half acid chloride of benzyl alcohol and phosgene (benzyl chloroformate).



This compound reacts with an amino acid and protects the amino group while an acid chloride is made in the usual way. The acid chloride is put into reaction with another amino acid, after which the "carbobenzoxy" group is removed by catalytic hydrogenation. One of the advantages of this method of procedure is its avoidance of hydrolysis as a final step. The use of hydrolysis to remove the protecting group might involve also a partial destruction of the polypeptide links.



It is also possible to make an acid chloride from a halogen-acylated peptide similar to (A) (p. 725). This acid chloride may be condensed with a molecule of amino acid or with a polypeptide, thus allowing the formation of long chains. It was by this process that Fischer built the large molecule mentioned below.

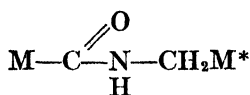
Inspection of the molecule of a simple amino acid such as glycine shows that it has the structure x-R-y which has been shown to lead to formation of polymers or ring compounds (see page 241). The ring formation has already been mentioned. Glycine not only forms a diketopiperazine ring compound, but under anhydrous conditions it can form chain compounds of high molecular weight. If heated in glycerol it gives a horn-like polymer which is evidently a high weight polypeptide; this may again be hydrolyzed to glycine.

If we could know in what order the amino acids are joined in any given protein it would be theoretically possible to build it after the manner just shown; practically the experimental procedures become too difficult.\* It was however possible for Emil Fischer to unite eighteen amino acids into one molecule in this way. The compound (an octadecapeptide) was L-leucyl-triglycyl-L-leucyl-triglycyl-L-leucyl-octaglycyl-glycine. This substance had a molecular weight of more than 1200, formed a colloidal solution in water, and responded to many of the tests for simple proteins. As the average molecular weight of the amino acids from proteins is around 140, and the molecular weight of a protein may be about 35,000 or 70,000 or much higher, the Fischer synthesis, while a brilliant achievement, must be considered as only a beginning.

However it renders assurance that in simple proteins, at least, the amino acids are joined by union of carboxyl and amino groups as in the amides. This union is known as the peptide link:

\* The amino acids of proteins are optically active, therefore it would also be necessary to unite the *proper isomers* in the proper order in synthesizing a natural product.





It will be seen that in the synthesis of a polypeptide free amino groups, which are primary amines, are changed to secondary amines. Similarly the carboxyl groups of the amino acids are neutralized when a polypeptide is formed.

We may test these conclusions by trying the action of nitrous acid. As will be remembered, this reagent liberates nitrogen from primary amino groups. The results of this test (called the Van Slyke test), show that during hydrolysis there is a steady increase in the number of free amino and free carboxyl groups, which reaches a maximum with the complete hydrolysis of a protein.

A protein largely made up of monocarboxy-diamino acids would be expected to show basic properties due to the presence of many free amino groups. An example is found in the protamines which are basic and which on hydrolysis yield a high percentage of basic amino acids. A protein largely built from dicarboxy-monoamino acids should have many free carboxyl groups. Zein is such a protein. It reacts with bases, not with acids; on hydrolysis it gives a high percentage of glutamic acid.

A protein containing a reasonable percentage of both types of amino acids (acidic and basic) should be amphoteric. Most of the water-soluble proteins are amphoteric.

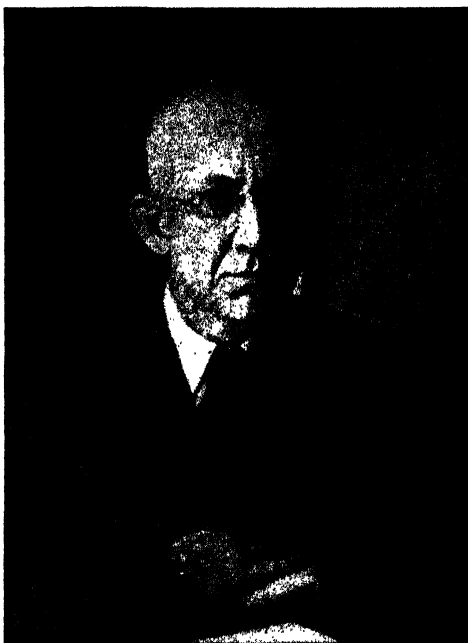
The free acid and basic groups in proteins are held responsible for the ability to form salts with either acids or bases. The same behavior was discussed in connection with individual amino acids (page 715). In the presence of acid, the amino acid binds proton and gives a positive ion which drifts toward the cathode when an electric current is applied. In presence of base, the amino acid loses proton of the carboxyl group, thus yielding a negative ion which drifts toward the anode. Proteins show the same behavior. At the isoelectric point there is no drift. At this point a protein is least soluble and most easily precipitated.

**Recent Experimental Work.** Experiments with thin films of protein have given an insight into the possible dimensions of these films, and of the valence forces operating between them. (See Reference 19.) The structure of such films (according to one theory) is presumed to follow from the "cyclization" of polypeptide units into "hexagons within hexagons." A complete protein would then be a series of such layers or films, or a space-enclosing molecule made by the infolding of one layer (see References 17 and 18 and Fig. 102).

The chains of polypeptides were formerly supposed to have their individual amino acids in a haphazard order of sequence, but this idea has been

\* See footnote, page 145.

HOMER ADKINS. (American, 1892- .) Professor of chemistry in the University of Wisconsin. Adkins' interest lies in the fields of catalysis and organic synthesis. Author of numerous papers on catalytic hydrogenation of organic compounds. Co-author of both text and laboratory manual of organic chemistry.



JAMES B. CONANT. (American, 1893- .) His work with chlorophyll is outstanding. In addition he has been interested in the quantitative side of organic chemistry. Work with free radicals, oxidation and reduction of organic compounds. He is author of several well known organic chemistry texts. He was chairman of the Division of Chemistry and is now president, of Harvard University. See *J. Chem. Education*, 9, 579 (1932).

*Photograph by Backrach.*

attacked. It is supposed that the amino acids of the chain recur at regular intervals in the chain; also that the total number of amino acids in a simple protein is 288 or a whole number multiple of 288 (see Reference 23). The original papers cited should be consulted to get a full conception of the fascinating picture of protein biosynthesis which they present and which cannot be given here on account of space limitations.\*

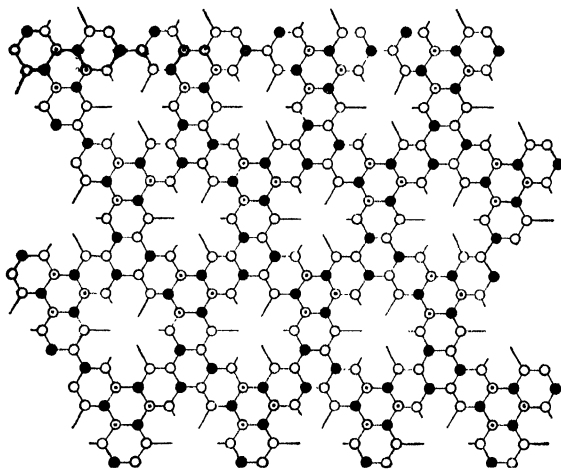


FIG. 102.—The cyclol pattern (see reference 18). The median plane of the lamina is the plane of the paper. The lamina has its "front" surface above and its "back" surface below the paper.  $\bigcirc$  = C(OH); peptide hydroxyl upwards.  $\bullet$  = N.  $\odot$  = C(OH); peptide hydroxyl downwards.  $\bigcirc$ — = CHR; direction of side chain initially outwards.  $\bigcirc$ — = CHR; direction of side chain initially upwards.

### COMPLEX PROTEINS

The proteins considered in the above discussion of structure are simple in nature. Their hydrolysis yields amino acids only. However we have indicated that many proteins give other substances besides amino acids when hydrolyzed. Carbohydrates, nitrogen bases, phosphoric acid, and other compounds are liberated when these complex proteins are subjected to hydrolysis. (See table, page 712.)

The nucleoproteins may be used for an illustration. Hydrolysis of a nucleoprotein yields finally:

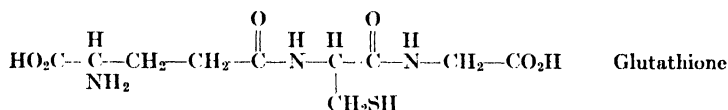
- (1) A carbohydrate (pentose derivative).
- (2) Purine bases, such as guanine or adenine (page 649).
- (3) Pyrimidine bases, such as thymine, cytosine (page 647).
- (4) Amino acids.
- (5) Phosphoric acid.

\* The conflict of theory reported here should be of particular interest to those students who plan to study biochemistry.

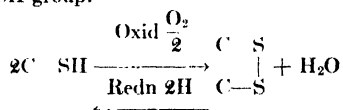
The great complexity of such substances is at once apparent. The synthesis of simple proteins awaits a knowledge of the optical isomers concerned, and the order and manner in which the amino acids are joined together, as well as assurance that all of the amino acids present in the proteins have been identified. The problem of synthesis of the complex proteins is naturally of still greater magnitude.

### GLUTATHIONE

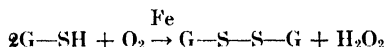
A tripeptide of especial interest is  $\gamma$ -glutamyl-cysteyl (cysteinyl)-glycine, known as glutathione; it is found in all active animal tissues.



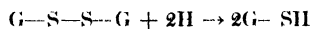
It has recently been synthesized in the laboratory. Glutathione, like cysteine, is easily oxidized and recovered. The reactions of cysteine may be shown as follows, letting C represent all of the molecule save the SH group.



Similarly the oxidation of glutathione may be shown as:



The oxidized molecule may act as a hydrogen acceptor, thus oxidizing another compound:



In this fashion the molecule may act as a go-between in biological oxidations.

Vitamin C (ascorbic acid) is also easily oxidized and again reduced, and may also be utilized in the body as a go-between in carrying on necessary oxidations.

**Industrial Importance of Proteins.** The role of protein for food has long been recognized. It not only supplies energy by its breakdown as do also the fats and carbohydrates, but is an essential constituent of all living cells. The protein of animal cells of skin, muscle, hair, etc., has a function parallel to that of cellulose in the plants. There is a profound difference between the food classes in that one may find a certain carbohydrate or type of fat in a wide variety of plant and animal cells, while the protein is more apt to be unique and characteristic of the particular locale in which it is found.

The demand for protein food is the mainstay of important industries (slaughtering, meat packing, cheese making, fishing). In addition we note the following applications of protein materials: (1) tanning of hides to form leather, (2) cooking of hide, tendon, and bone scraps to make gelatin and glue, (3) processing of casein to make glues, paints, synthetic wool fiber, plastics (with formaldehyde), (4) use of wool and silk for textile manufacture.

## REVIEW QUESTIONS

1. Write the graphic formulas for alanine, norleucine, leucine, cystine, lysine, tyrosine, and indicate the asymmetric carbon atoms in these compounds. Which of the aliphatic amino acids on pages 246 and 277 do not have asymmetric carbon atoms?
2. Suggest a method of synthesis for norleucine, and for  $\alpha$ -aminobutyric acid.
3. By what means could alanine be changed to lactic acid?
4. How could phenylalanine be distinguished from  $\alpha$ -hydroxy- $\beta$ -phenyl-propionic acid?
5. By what procedure could one show that the two nuclear groups in tyrosine are *para* to each other?
6. Show the synthesis of glycyl-glycine by two different methods.
7. Write equations for the synthesis of alanyl-alanine.
8. Write the formulas of the following:
  - (a) Alanyl-glycyl-leucine.
  - (b) Leucyl-glycyl-alanine.
9. How many optical isomers are theoretically possible for:
  - (a) Glycyl-alanine?
  - (b) Alanyl-alanine?
10. Review the methods for the preparation of  $\alpha$ -amino acids.
11. Indicate the steps needed to synthesize a tripeptide.
12. Define isoelectric point; zwitterion.
13. Show the synthesis of *i*-phenylalanine by the malonic ester method.
14. Give graphic formulas and names for: (a) Two monocarboxymonamino acids derived from proteins; (b) One hydroxymonoamino acid; (c) Two sulfur-containing amino acids; (d) Two monocarboxydiamino acids; (e) One monoaminodicarboxy acid; (f) One aromatic amino acid; (g) Two heterocyclic amino acids.
15. Which amino acids if combined in "acid amide" linkage would give polypeptides with free amino groups?
16. Which amino acids if combined in "acid amide" linkage would give polypeptides with free carboxyl groups?
17. Write the formula for the sodium salt of alanine, for the hydrochloride of alanine, and for the zwitterion form of the free acid.
18. If a protein were completely hydrolyzed and with no loss of materials, would the combined weight of all the hydrolysis products be equal to the original weight of protein or less or more than this weight? Why? What is the weight relationship which ordinarily obtains in such a hydrolysis? Why?
19. A certain monoamino acid upon nitrous acid treatment yields 30 cc. of nitrogen from a sample of acid weighing 0.1755 g. What is the molecular weight of the acid? Could the compound be any of those listed in this chapter?
20. Give chemical facts which support the theory that a simple protein is made up of  $\alpha$ -amino acids joined by "peptide" links.
21. Oxyhemoglobin contains 0.34% of iron. If we assume that there is one atom of iron in the molecule, what molecular weight of oxyhemoglobin follows from the use of the "chemical method"?
22. If we learn by analysis the percentage of a certain amino acid in a given protein, how can we use this information to estimate the molecular weight of the protein?
23. The large synthetic polypeptide made by Emil Fischer (page 727) was hydrolyzed by both trypsin and erepsin. This fact is considered highly significant in connection with a comparison of this synthetic material and a simple natural protein. Wherein lies the importance?
24. In the precipitation of a protein by a complex acid such as tannic acid, the protein combines with the complex anion of the acid. Should the solution be acid or alkaline to cause this to take place?

25. Discuss the industrial importance of proteins.
26. Explain how such a compound as glutathione can act as a "go-between" in oxidation of other compounds.
27. List the protein amino acids in groups which show basic, neutral, and acid reactions, respectively.
28. How can the amphoteric properties of proteins be explained?
29. Define the following terms: (a) Conjugated protein; (b) Derived protein; (c) Indispensable amino acid.
30. List the color reactions of proteins, describe each briefly, and tell for what grouping each is specific.

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## GLYCOSIDES, ENZYMES, HORMONES, VITAMINS

## GLYCOSIDES

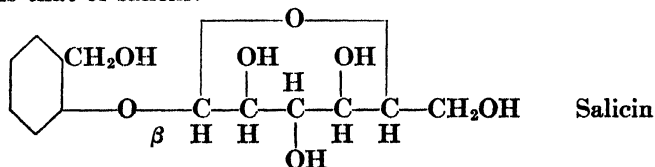
Glycosides are naturally occurring substances found in plants, usually in small amounts. They derive their class name from the products of their hydrolysis, which generally include glucose, although other sugars have been found in some of the glycosides (arabinose, ribose, xylose, galactose, mannose, fructose, rhamnose).

**Properties.** Glycosides are usually water-soluble and are obtained from plants by extraction. The plant enzymes, which would cause hydrolysis of the glycoside, are first inactivated by heat. Many such enzymes occur in plants, each being specific for the hydrolysis of a particular glycoside. However emulsin, which is found in bitter almonds, causes hydrolysis of many of the glycosides.

Glycosides are for the most part colorless crystalline solids, mostly levorotatory, and possessing a bitter taste. They occur in the roots, bark, fruit, and leaves of plants.

Glycosides may be hydrolysed by acids, and also by the aid of the enzymes (see next section). It is noteworthy that in the plants the particular enzyme which catalyzes the hydrolysis of the plant glycoside is always contained in the plant, although it is stored apart from the glycoside in other cells.

**Structure.** The hydrolysis products of glycosides include, in addition to the sugar, phenolic compounds such as hydroquinone, saligenin (*o*-hydroxybenzyl alcohol) or phloroglucinol; aldehydes, esters, acids, mustard oils, etc.; usually compounds of the aromatic series.\* The union of the sugar with the phenolic compound in the glycoside is presumed to be the same as that occurring in the simple glucosides formed from methyl alcohol and glucose (see page 362). Natural glucosides appear to have the *beta* structure, while synthetic glucosides of both *alpha* and *beta* types have been made. In laboratory experiments with glucosides of known structure, it is found that emulsin splits *beta* glucosides but not *alpha* glucosides. A typical structure is that of salicin:



\* The non-sugar part is called the *aglycon*.



**Uses. Significance.** A number of the glycosides have a strong physiological action which leads to their use in medicine; important dyes may be obtained from others (see indigo, page 693, alizarin, page 692). In the plant the glycosides may serve several purposes. Their bitter taste may keep birds and animals from eating seeds and fruits before they have come to full term. This theory seems plausible, since as the fruits ripen and the plants mature their seeds, the glycosides commonly disappear. Those glycosides which occur in flowers are often of striking color; they probably serve to attract insects to the flowers and so aid in cross-pollination.

The phenolic compounds and acids contained in the glycosides have an antiseptic and bactericidal action. When a plant tissue is bruised, the enzyme material in the plant is thrown together with the glycoside, causing its hydrolysis. The consequent liberation of the antiseptic would prevent decay at the seat of the injury. Further, it has been stated that certain harmful drugs are removed from the human body as glycosides (page 363). In the plant the situation may be somewhat the same; the glycoside may illustrate a transformation of materials toxic to the plant into less harmful forms. The truth of one of these theories does not necessarily negative the others; it is possible that the glycosides serve the plants in several of the different ways suggested and in other ways.

Several hundred glycosides have been isolated and studied. In the following list are a few representative compounds of the various groups of these substances.

*Sinigrin*,  $C_{10}H_{16}O_9NS_2K \cdot H_2O$ , found in black mustard seed, is hydrolyzed by the enzyme myrosin to glucose, allyl mustard oil, and potassium hydrogen sulfate.

*Amygdalin*,  $C_{20}H_{27}NO_{11} \cdot 3H_2O$ , found in bitter almonds, peach kernels, etc., hydrolyzed by emulsin to benzaldehyde, glucose, and hydrogen cyanide.

*Arbutin*,  $C_{12}H_{16}O_7 \cdot \frac{1}{2}H_2O$ , found in bearberry leaves, hydrolyzed by emulsin to glucose and hydroquinone. This glucoside is used in medicine.

*Salicin*,  $C_{13}H_{18}O_7$ , found in leaves and bark of the willow. Hydrolyzed by emulsin or ptyalin, to glucose and saligenin. It is used as a remedy for rheumatism. Saligenin is used as a local anesthetic.

*Ruberythric acid*,  $C_{26}H_{26}O_{13}$ , is obtained from the madder root. It may be hydrolyzed to glucose and alizarin.

*Populin*,  $C_{20}H_{22}O_8 \cdot 2H_2O$ , is found in poplar tree bark. It is hydrolyzed to glucose, saligenin, and benzoic acid. The substance has antipyretic action.

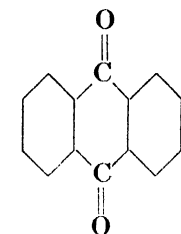
*Phloridzin*,  $C_{21}H_{24}O_{10} \cdot 2H_2O$ , is found in the bark of trees (pear, cherry, apple). It is hydrolyzed by acids to glucose and phloretin, which in turn gives phloroglucinol. Phloridzin when injected or swallowed produces glycosuria and a temporary condition much like that observed in a form of diabetes. Its use with dogs has helped in the study of metabolism.

*Tannins* mentioned on page 530 should also be included as a special class of glycosides. See also indigo, page 693.

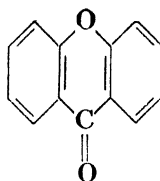
The *digitalis glycosides*, obtained from the leaves and seeds of the fox-glove, are used in medicine; several have value as cardiac stimulants.

### FLOWER PIGMENTS

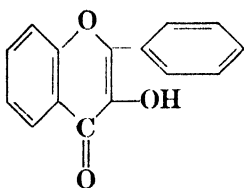
The red, blue, and yellow colors of flowers and other parts of plants have been shown to belong to the class of glycosides or to be formed from them. They therefore pertain to this discussion though it is impossible to give them more than a brief mention. They are derivatives of complex ring systems of the several types shown below:



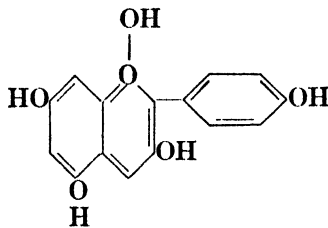
Anthraquinone  
(Red derivatives)



Xanthone  
(Yellow derivatives)



Flavonol (Yellow  
derivatives)



Anthocyanin nucleus  
(Red, blue, and  
violet derivatives)

A general similarity of structure will be noted in these formulas. Each has a "condensed" benzene ring and each has an integral oxygen or keto group, or both, in a ring. The natural derivatives are hydroxylated compounds. Several are mentioned in the chapter on dyes, page 701.

### ENZYMES

In carrying out various chemical transformations, both in the realm of inorganic and of organic chemistry, it has often been noted that reactions which normally proceed at a slow rate may be greatly speeded up by the use of catalysts. The employment of these catalysts makes certain processes commercially feasible which would not otherwise be so. For example, aluminum chloride catalyzes the loss of hydrogen chloride in the Friedel-

Crafts reaction, various oxides aid in dehydration reactions, acids and bases assist in hydrolysis, etc.

In the life cycle of plants and animals these same processes of hydrolysis, synthesis, oxidation, and reduction must be carried out at temperatures which are low in comparison with those of the laboratory, and in nearly neutral media. The substances which catalyze these reactions in nature are known as enzymes. Enzymes are elaborated by living cells. Those which act only within the cell, and which are obtained for study by rupturing and destroying the cell wall, are the "intracellular enzymes." Others which are secreted by cells and act outside of them are the "extracellular enzymes."

**Enzymes as Catalysts.** In its capacity as catalyst an enzyme conforms to our ordinary definition of the term. Thus (1) it increases the speed of a certain reaction; (2) the amount of increase in speed is proportional to the amount of enzyme present; (3) the enzyme is not itself a part of the reaction product (though it is apt to be partially destroyed during its action); (4) small amounts of enzyme affect large quantities of material, in some cases as much as a million times the weight of enzyme employed. Enzymes resemble inorganic catalysts in that they often catalyze both a hydrolysis and a synthesis. Thus a lipase which aids in the hydrolysis of fats to fatty acids and glycerol, can also promote the synthesis of an ester in the laboratory. Similarly, maltase and emulsin have been used in the synthesis of glucosides. Enzymes differ from inorganic catalysts in that their action is specific. In a number of cases a certain enzyme will catalyze a specific reaction and none other. In more cases the enzyme will act on a certain group of compounds alone. Thus a fat-splitting enzyme does not affect proteins. Maltase splits only  $\alpha$  glycosides; emulsin only those of  $\beta$  structure (pages 374, 735, 740). Though we conceive of enzymes as catalysts, it is also agreed that they have the power to initiate chemical reactions.

**Properties of Enzymes.** Enzymes are colloidal substances of high molecular weight and great complexity, whose purification is rendered difficult by their readiness to adsorb foreign substances, a common habit of colloidal materials. Many enzymes are precipitated from their solutions by salts, such as sodium sulfate or ammonium sulfate, or by strong alcohol.

**Enzymes as Chemical Entities.** When alcoholic fermentation was first studied, it was believed that the process was in some way bound up with the life activities of the yeast plant itself. This idea was abandoned after Buchner in 1897 succeeded in grinding yeast with sand, and extracting therefrom a liquid which was effective in promoting the fermentation. The substance in the juice responsible for the catalytic action was called zymase.

Although the exact nature of the enzymes is not known we believe them to be definite compounds, whose reactions conform to their structures. This opinion has been strengthened by the isolation of urease in crystalline form, the first instance of the isolation of a pure enzyme. Other crystal-

line preparations include pepsin, trypsin, amylase, and catalase. All are protein-like in their properties; many chemists believe that they are proteins.\*

One view of enzymes is that they consist of a colloidal carrier and specific chemical groupings. It is thought that these active groups may be shifted from one carrier to another. The catalytic activity is laid to the carrier, but the specificity of the enzyme is thought to reside in the active groupings. Between such groups and others in the material to be acted upon exists a close relationship often called the "lock and key" relationship. A chemist would rather conceive of the enzyme as a definite entity, ultimately capable of laboratory synthesis. If they are actually proteins such synthesis would be difficult to say the least, while if a much simpler "active group" is to be synthesized, there would be more hope of success.

**Factors Affecting Enzyme Activity.** The action of enzymes is strongly influenced by their environment. At or near  $0^{\circ}$  very little action takes place, while temperatures in excess of  $60^{\circ}$  cause their rapid deterioration. In solution all are inactivated at temperatures from  $70^{\circ}$  to  $100^{\circ}$  although in the dry state they will bear heating to this point. The optimum temperature for their activity depends upon two factors. A rise in temperature increases the catalytic activity but may also increase the rate of destruction of the enzyme. Hence if the reaction is to go on for some time a moderate temperature would be optimum. Nature has adjusted this to suit the needs of the occasion. The optimum *pH* for enzyme action lies between the limits 4 and 8; certain enzymes work better in slightly acid media, others function better under alkaline conditions. However the range of the optimum *pH* of an enzyme is usually small. Some enzymes require the presence of acid or a salt for their activity while others require a definite compound or "coenzyme." Thus pepsin as it is formed by the gastric cells of the stomach is incapable of digesting protein. In presence of acid (*pH* 2.0) it becomes active. Phosphates are needed for the change of sugar to alcohol and carbon dioxide. Many substances inhibit the activity of enzymes (antipepsin of gastric mucosa). Salts of heavy metals are generally inhibitory.

**Classification and Nomenclature.** Enzymes are grouped under various headings, according to the reaction which is catalyzed and the nature of the substrate. Most of them are hydrolases. Within this class are those acting on proteins (proteolytic enzymes), etc. In addition are those which act upon amino group (deaminases), those which promote oxidations (oxidases), and others. The names of most enzymes repeat the name of the substrate (substance upon which they act) to which is added the suffix "ase." A few enzymes retain their old names (pepsin, trypsin) which do not fit into the general scheme. In the following list the more common enzymes are included, together with the substrate and mode of action of the enzyme.†

\* See Hawk and Bergeim, *Practical Physiological Chemistry* (Blakiston, 1937), page 243 ff.

† The list is not complete.

**Hydrolyzing Enzymes. Hydrolases.**

*Carbohydrases.* (a) Amylases. Malt amylase found in germinating grain. Ptyalin of saliva. Starch to maltose.

(b) Sucrase of intestinal juice. Inversion of sucrose.

(c) Maltase of malt, yeast, and intestinal juice. Maltose to glucose.

(d) Lactase of intestinal juice. Lactose to glucose and galactose.

(e) Emulsin, which is very widely distributed in nature, chiefly in bitter almonds, is able to hydrolyze many natural glucosides, also synthetic glucosides. An interesting observation is that maltase, which is also able to hydrolyze glucosides, only affects those having *alpha* structure, whereas emulsin hydrolyzes only the *beta* synthetic glucosides. As we have said, many natural glucosides are hydrolyzed by emulsin; it is therefore reasonable to consider that these have the *beta* structure, as was previously stated

*Lipases and Esterases.* Lipase, steapsin, in the pancreatic juice, hydrolyzes fats to fatty acids and glycerol.

*Proteases.* (a) Pepsin, found in gastric juice, aids in the change from protein to proteoses and peptones.

(b) Trypsin, in the pancreatic juice, converts proteins, proteoses, and peptones to simple polypeptides and amino acids.\*

(c) Erepsin, secreted by the intestine, changes proteoses and peptones to amino acids.\*

(d) Rennin, in gastric and pancreatic secretions. Casein to paracasein.

Among the **fermentation enzymes** we note zymase, found in yeasts, which catalyzes the oxidation and reduction of glucose to carbon dioxide and alcohol.

**Oxidases** catalyze oxidations (ethanol to acetaldehyde, aldehydes to acids). Catalase induces the change of hydrogen peroxide to oxygen and water. It is contained in the blood and in tissues (liver, kidney, muscle, etc.).

**Dehydrogenases**, found in many tissues, aid the oxidation of organic compounds within the body by removal of hydrogen atoms.

**Uses of Enzymes.** Enzymes have a considerable commercial importance which will be seen in the following incomplete list of applications: tanning (bating of skins), textiles (degumming of silk, etc., preparation of soluble starch finish), preparation of alcohols and beverages, of cheese.

The importance of enzymes in the life of plants and animals can hardly be realized. The number of different chemical changes which take place in a body cell at any time must be large, and there is reason for supposing that many of these reactions would not proceed at measurable rate without the help of enzymes. Again, the number of enzymes in the organism must be equally great as the number of reactions to be promoted. Many different enzymes have actually been found in the animal organism. It should be apparent that the study of enzymes to determine their nature and the

\* Trypsin and erepsin have been found to consist of several individuals. They are not simple as was formerly supposed.

manner in which they act is highly important. The growth of our knowledge along these lines will hasten the time when we may imitate the highly efficient organic syntheses now carried on by the plants.

## HORMONES

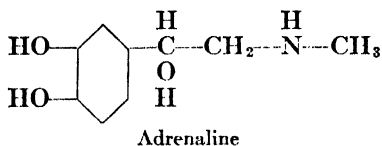
Hormones or chemical messengers (name from Greek, to excite) are chemical substances elaborated by the ductless and other glands of the body and sent into the blood. Their function appears to be the control of various bodily activities, and their action suggests that of enzymes in being specific and extremely powerful.

Productive chemical work in the hormone field may be dated from 1902, when Bayliss and Starling showed that the flow of the pancreatic juice was controlled by a substance which could be obtained from extracts of duodenal mucous membrane. They called the substance *secretin*, and coined at that time the word hormone, which has since been applied to similar active compounds.

The body is well supplied with ductless glands, and the chemical compounds which they liberate to the blood are evidently of great physiological significance. Over- or underactivity of these glands is usually followed by profound disorders and diseases.

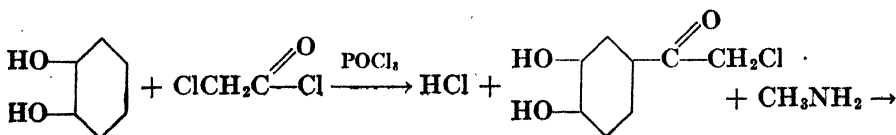
The field of hormone research is fascinating to the chemist because of its difficulties, and because of the certainty that every positive finding will benefit mankind. Within late years progress has been rapid, with many of the best chemists here and abroad devoted to the problems of structure and synthesis. The material given here will include only those formulas which appear to be well established.

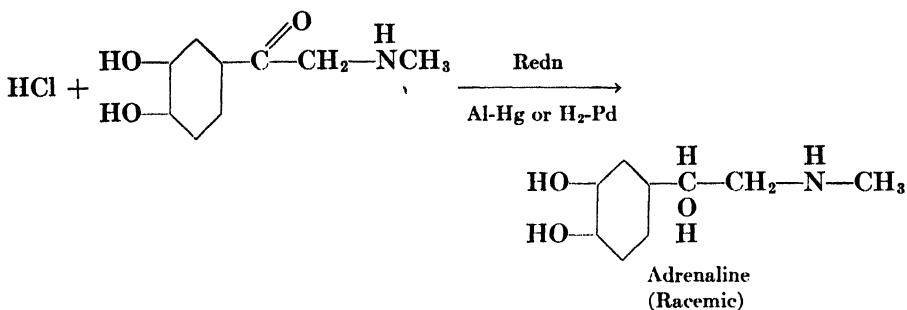
**Adrenaline** (epinephrine) is obtained from the medulla of the suprarenal glands, and is also artificially prepared as indicated below. Its action is to increase blood pressure by constricting the capillaries. In medicine it is used to check bleeding in minor operations, in the treatment of asthma.



The pure natural compound was first isolated in 1901 (Aldrich and Takamine).

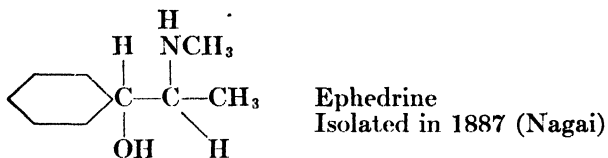
Synthesis of adrenaline (Stolz and others, 1904):



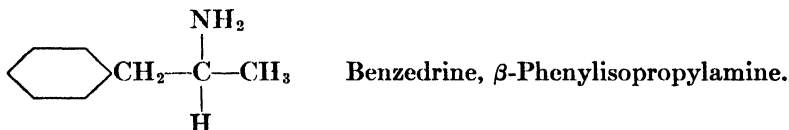


When adrenaline is made in the laboratory the racemic product is, of course, obtained. This is separated into the *d*- and *l*-isomers by crystallization of the tartrates. The *l*-modification is natural adrenaline, while the *d*- is only one-twelfth as active.

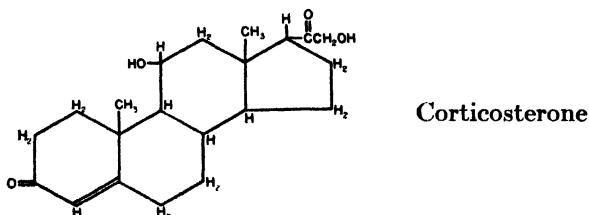
**Ephedrine**, a compound obtained from the Chinese plant *Ma Huang*, has an action like that of adrenaline; it is also used as a mydriatic. It is more stable to oxidation than adrenaline, and has the added advantage that it is effective when given by mouth. As there are two asymmetric carbon atoms, four isomers are known. All have been synthesized.



A synthetic compound, *Benzedrine*, has been made to substitute for ephedrine and adrenaline in certain instances. It has a stimulating effect on the central nervous system and raises blood pressure.\*

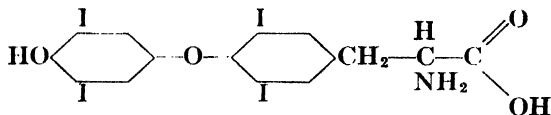


The cortex of the adrenal gland contains hormones of great importance. One of these is *corticosterone*.



\* It should be noted that neither ephedrine nor benzedrine is a hormone, though it was proper to discuss them here because of their similarity to adrenaline.

***l*-Thyroxine**, which is obtained from the thyroid gland, has been isolated by Kendall, and later by Harington, who assigned to it the following structure:

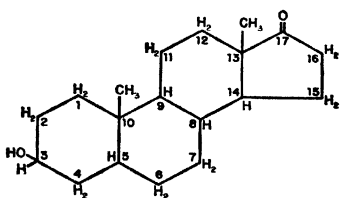


This hormone is used in medicine in the treatment of thyroid insufficiency, cretinism, obesity, etc. Like adrenaline, it has been artificially synthesized (1927) and separated into the optical isomers. The *l*-isomer (natural compound) is three times as active as the *d*-.

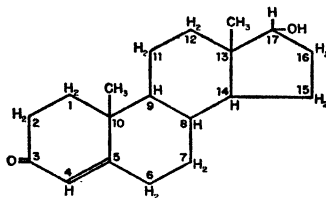
**Insulin.** The isolation of insulin by Banting, Best, and others has been well publicized. This pancreatic hormone regulates carbohydrate metabolism. It has been used with striking success in the treatment of diabetes. Insulin has been prepared in crystalline form. Hydrolysis yields amino acids such as come from the hydrolysis of proteins, moreover it gives the usual tests characteristic of a simple protein. Like a protein it is digested when given by mouth and must be injected. The assumption created by these findings has been confirmed by recent work, which proves the peptide structure of insulin; it has been shown to be an albumin.

#### SEX HORMONES

**Male or Androgenic Hormones.** Androsterone has been isolated from male and female urine and from the testicles of animals. It is found to affect the secondary sexual characteristics (growth of comb in capons, for example). Testosterone is about ten times as active as androsterone.

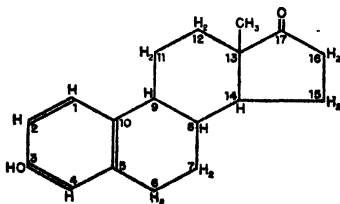


Androsterone  
 $C_{19}H_{30}O_2$   
Isolated in 1931  
(Butenandt)



Testosterone. Properties  
similar to those of andro-  
sterone.  $C_{19}H_{28}O_2$   
Isolated in 1935 (Lacquer)

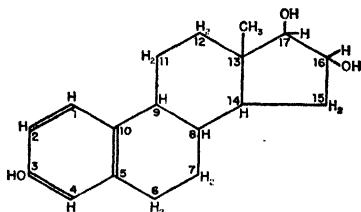
**Estrogenic Hormones.** Several compounds have been isolated from human and equine pregnancy urine.



Estrone, Theelin, estro-  
genic ovarian hormone.  
(Greek, Theelys = female).  
 $C_{18}H_{22}O_2$   
Prepared in 1929  
(Doisy, Butenandt)



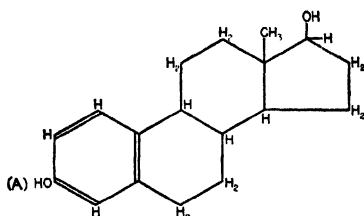
Estrone has also been found in palm nut oil and in male urine. It has a definite stimulating action in the female (growth of uterus, secondary sexual characteristics).



Estriol, Theelol, estrogenic hormone.  $C_{18}H_{24}O_3$   
Isolated in 1930  
(Marrian)

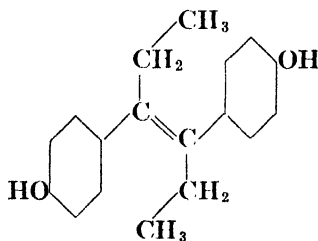
Estriol, distilled under vacuum with potassium hydrogen sulfate, loses water and yields estrone and an isomer. Its action is like that of estrone but weaker.

The reduction of estrone gives estradiol which is from four to eight times as active as estrone. The compound was made in the laboratory (1933) previous to its isolation from the ovary (1935). It and its benzoic acid ester are used in medicine.

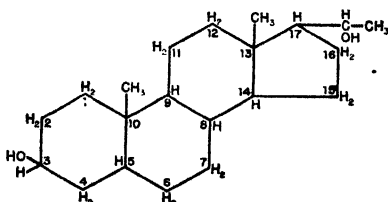


Estradiol. The benzoate is formed at position (A)

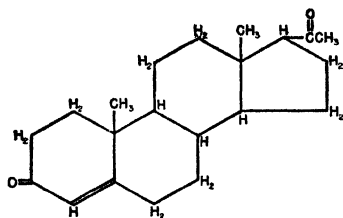
An important synthetic estrogenic compound is diethylstilbestrol, whose formula is presented here in such a way as to show its structural likeness to estriol.



Diethylstilbestrol



Pregnanediol, non-estrogenic.  
The corresponding diketone is pregnanediolone.  $C_{21}H_{34}O_2$ .  
Isolated in 1929 (Marrian).  
In the human body pregnanediol is formed from progesterone.

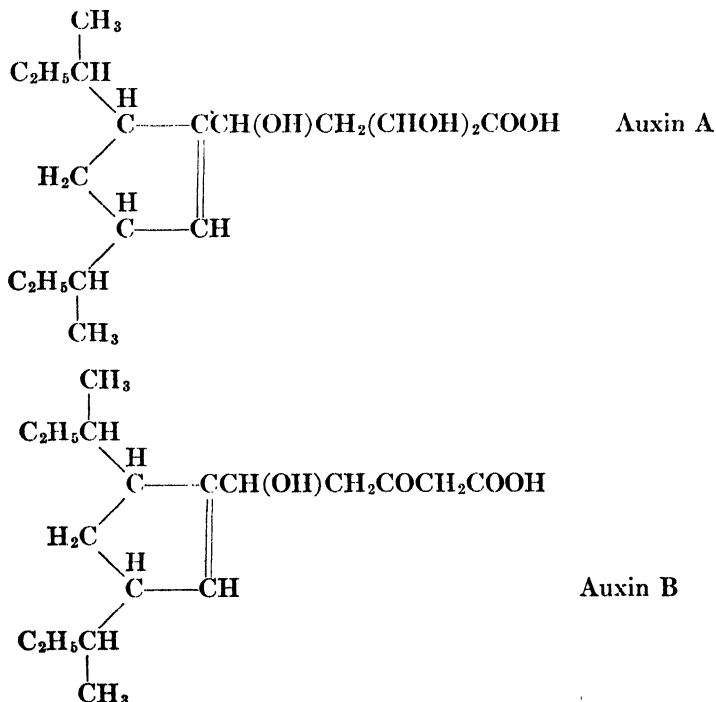


Progesterone. Corpus  
luteum hormone.  $C_{21}H_{30}O_2$   
Isolated in 1934

The structures of these compounds show great similarity to each other. They are also similar in make-up to sterols, such as cholesterol (page 752). A resemblance is also noted between them and the carcinogenic hydrocarbons (page 599).\*

The isolation and synthesis of sex hormones are accomplishments of recent years, already of great aid to medical practice. A number of different hormone preparations have been made from the pituitary gland and parathyroid glands. These are not yet sufficiently characterized for inclusion here.

**Plant Hormones.** Substances called auxins, isolated from plants, have been found to play the part of hormones therein. One of the effects of such substances is to cause bending of leaves or stems after local application. Formulas of Auxin A and Auxin B are given below.



\* The relationship between these substances and others built on the "cholane" ring is strikingly illustrated in the table in Hack's *Chemical Dictionary* (Blakiston, 1944, p. 196).

Synthetic compounds have been made which are especially effective in promoting root growth, also growth without pollenization. These are of value in plant nurseries (see page 651).

TABLE 50.—HORMONE DATA\*

Name	Formula	M.p., °C.	$[\alpha]_D^{20}$	Oxime, M.p., °C.	Semi- carbazone, M.p., °C.	Acetate, M.p., °C.
<i>l</i> -Adrenaline . . .	$C_9H_{13}NO_3$	Dec. 207-11	— 53	Hydrochloride, 157°		
<i>l</i> -Ephedrine . . .	$C_{10}H_{15}NO$	40 B.p. 255	— 6.3	Hydrochloride, 218		
Benzedrine . . .	$C_9H_{13}N$					
Thyroxine . . .	$C_{15}H_{11}NO_4I_4$	232 Dec.				
Androsterone . . .	$C_{19}H_{30}O_2$	182-3	+ 94.5	216	276°	161°
Testosterone . . .	$C_{19}H_{28}O_2$	154	+109	222-3	...	140-1
Estrone . . .	$C_{18}H_{22}O_2$	259	+158.5	233	259	126
Estriol . . .	$C_{18}H_{24}O_3$	280	+ 30	.....	...	Triacetate, 127
Pregnanediol . . .	$C_{21}H_{36}O_2$	235	.....	.....	...	183
Progesterone . . .	$C_{21}H_{30}O_2$	121 (128)	+192	Dioxime, 243		

\* See note regarding ephedrine and benzedrine, page 742.

### VITAMINS

As early as 1905, workers in the field of animal nutrition expressed the view that a diet composed of pure fat, carbohydrate, and protein is inadequate for life, and even with the addition of inorganic factors is inadequate for health and vigor. It was recognized that certain as yet unknown substances must be added to the diet to maintain health and avoid deficiency diseases, such as scurvy.

Meantime Eijkman, studying the disease beriberi, came to the conclusion that it was caused by the monotonous diet of polished rice common to those afflicted by the disease. Beriberi was prevalent in parts of China, Japan, India, and in Java where Eijkman was stationed. It was shown that the disease could be relieved by restoring the rice polishings to the diet.

Birds fed on a diet of polished rice developed conditions similar to those of beriberi, and were cured by addition to the diet of the outer coats removed in the polishing. Later Funk prepared from yeast and from rice polishings a crystalline substance which had high curative value. He proposed the name *vitamine* for compounds of this kind, which has since been changed to *vitamin*, as the compounds are not amines.

Research in the vitamin field became active with these discoveries and has increased almost in geometrical ratio since that time (1910). The active compounds were given letter names by their discoverers since their

chemical structures were unknown at the time. Now we know the structures of several and find them to be quite different from each other. It seems better, however, to group these compounds than to place each in its proper chemical niche.

The vitamins, then, are compounds necessary, though in minute amounts, in our diet.\* They are not energy-producing compounds; neither are they used as building blocks for tissue construction. The name "Vitamin" has been proposed for compounds which are necessary in the same sense as the vitamins, and which may also be used to build tissue or supply energy. Vitamins are perhaps best likened to hormones. If that classification were adopted we would have two classes of hormones, those which can be synthesized in the body, and those for which we look to the plants. Vitamins may

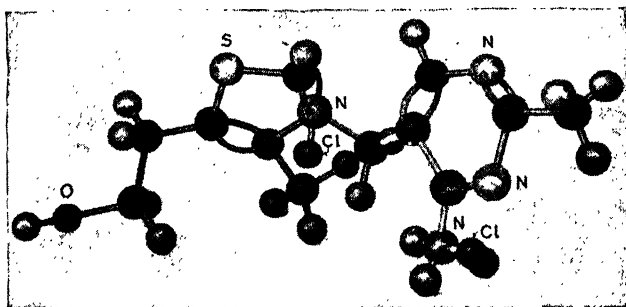


FIG. 103.—Model of B<sub>1</sub> molecule. (*Ind. and Eng. Chemistry.*)

be classified as fat-soluble and water-soluble. The first named dissolve in fats and in fat solvents. They are A, D, E. Vitamins B, C, are water-soluble.

**Vitamin A.** Two vitamins A are known; without doubt there are other compounds of this series which will be found later. The present discussion concerns the only one which has been isolated and synthesized. Lack of this vitamin is associated with the onset of eye diseases (xerophthalmia, night blindness, conjunctivitis) and is possibly responsible for a lessened resistance to infectious diseases. Growing rats given a diet lacking in A soon cease gaining in weight. They fail to reproduce and are short lived.

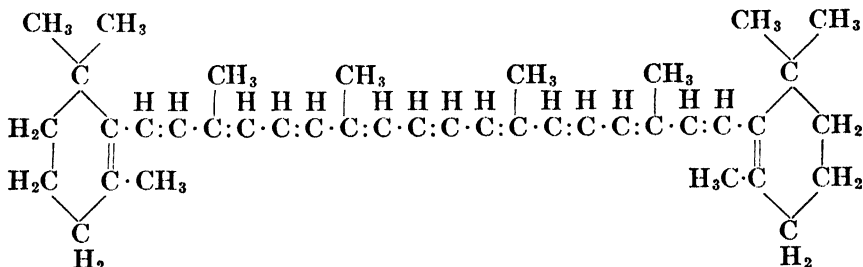
A good source of the vitamin is halibut-liver oil;† it is also found in cod-liver oil, butter, egg-yolk and (as carotene) in green vegetables and carrots. Carotene and vitamin A are fairly stable to heat and are not likely to be destroyed in the kitchen, however they suffer oxidation with relative ease,

\* Vitamins are synthesized by the plants and are apparently necessary for the healthy growth of plants. Animals other than man have equal need of vitamins but usually lack the ability to synthesize them. Individual animals have different vitamin necessities.

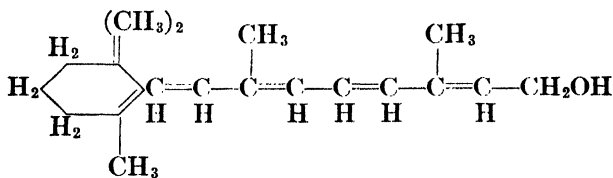
† A technique has now been developed for distilling vitamin A directly from fish oils. The distillation is conducted in a molecular still at very low pressure.

especially at elevated temperatures. Vitamin A gives a blue color with antimony trichloride.

It is found to have a structure closely related to that of the carotenoids, fat-soluble pigments found in plants. The formula for  $\beta$ -carotene is given below. Other substances with somewhat similar structure have been isolated, several of which, like this compound, yield vitamin A in the animal body.\*



$\beta$ -Carotene,  $C_{40}H_{56}$ . Vitamin A precursor. M.p.,  $183^{\circ}$ . Forms two molecules of vitamin A by dividing symmetrically. Note the recurring isoprene unit in the long chain.



Vitamin A,  $C_{20}H_{29}OH$

Attention is directed to the similarity of structure between vitamin A and irope (violet perfume). It is significant that the vitamin preparations also have this odor.

**Vitamin B.** What was originally called vitamin B has been shown to be a complex. Ten or more factors have taken its place to account for individual dietary effects. These have been variously named by investigators, so that some confusion exists in the terminology.

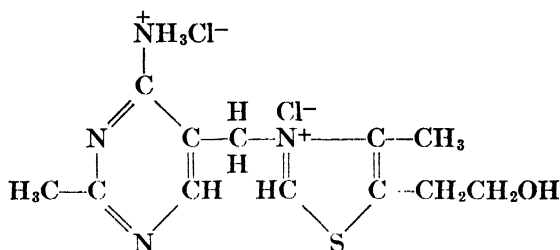
**B<sub>1</sub>. Antiberiberi Vitamin.** Growth-promoting. Water-soluble. Is found in yeasts, eggs, and in the hulls and germ of cereal grains. The highly milled white flour used for bread making is deficient.

B<sub>1</sub> exerts a definite influence upon lactation; successful lactation with rats depends upon an adequate supply. With humans, a lack of B<sub>1</sub> interferes with normal growth of children. Various nervous and digestive disorders have also been traced to lack of B<sub>1</sub>. There is also a relationship between B<sub>1</sub> and carbohydrate metabolism; diabetic patients have been benefited by use of the vitamin. Severe deficiency of B<sub>1</sub> causes the onset

\* Kuhn and Morris (1937) reported the synthesis of vitamin A. Baxter and Robeson (1942) presented photographs of the crystalline A and of several of its esters.

of beriberi. About 2 mg. of this vitamin per day appears to be adequate for human needs.

Vitamin B<sub>1</sub> is destroyed by heating in an autoclave to 120°, but is not harmed in ordinary brief cooking operations; it may, however, dissolve in the cooking water and be lost if this is rejected. A recent report indicates that commercial canning operations are very destructive. B<sub>2</sub> is more stable to heating than B<sub>1</sub>. The following formula has been established by the synthesis of the compound, in all respects identical with the natural vitamin.

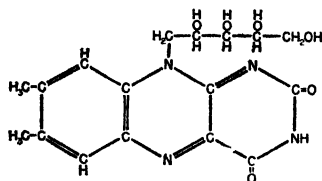


Vitamin B<sub>1</sub> hydrochloride, Thiamin chloride  
(Williams and Cline, 1936)

Expected U. S. synthetic production: 25-30 tons annually

Prices per ounce: 1935, \$8000; 1943, \$15

**Riboflavin, B<sub>2</sub> (G).** Growth-promoting. Water-soluble. The vitamin can be obtained from yeast or liver, egg-white, spinach. Lactoflavin, a pigment from milk, is identical with B<sub>2</sub>. Rats fed a diet deficient in B<sub>2</sub> develop baldness and cataract. Growth ceases and death soon occurs when no B<sub>2</sub> is fed. The structure has been worked out and the compound has been synthesized. Other compounds with similar gross structure have been made; some have activity similar to that of B<sub>2</sub>, though less intense. The daily adult requirement of B<sub>2</sub> is 2-3 mg.



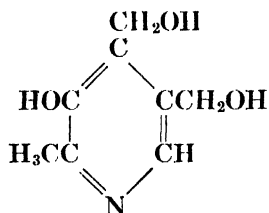
Riboflavin,  
(Lactoflavin),  
Vitamin B<sub>2</sub>  
Synthesized 1935  
(Kuhn, Karrer)

**B<sub>3</sub>.** This vitamin may be identical with pantothenic acid. It is water-soluble, necessary for weight increase with pigeons; present in liver, yeast, whole grains.

**B<sub>4</sub>.** Growth-promoting. Antiparalytic growth factor for rats. Occurs in yeast and liver.

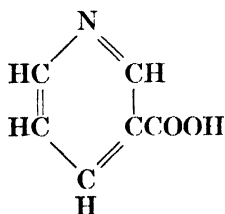
**B<sub>5</sub>.** Not yet well characterized. B<sub>5</sub> is a weight maintenance factor for birds. It is possibly identical with nicotinic acid, as the latter has properties attributed to B<sub>5</sub>.

**B<sub>6</sub>, Pyridoxin.** Rice polishings and yeast are good sources; also wheat germ. B<sub>6</sub> is water-soluble. With rats B<sub>6</sub> is growth-promoting and preventive of acrodynia (a dermatitis).

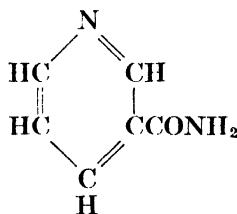


Vitamin B<sub>6</sub>, Pyridoxin  
Synthesized in 1939  
(independently in Germany and U. S. A.)

**Nicotinic Acid; Nicotinamide (P.P. Factor).** Good sources are wheat germ, liver, yeast. The compound was isolated from yeast and rice in 1912 by Funk; the first successful treatment of human pellagra was reported in 1937. Pellagra, however, is usually caused by lack of other B vitamins besides nicotinic acid, particularly B<sub>1</sub> and B<sub>2</sub>.

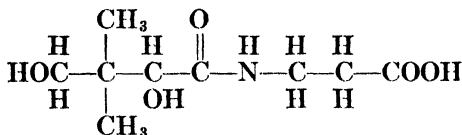


Nicotinic acid



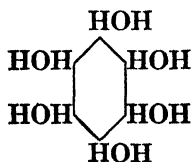
Nicotinamide

**Pantothenic Acid.** This vitamin is found in all animal tissues; liver and kidney are good sources, also molasses, rice bran. The vitamin is water-soluble; sensitive to heat, to acids and bases. The vitamin is growth-promoting for rats. Chicks on a deficient diet develop a dermatitis.



Pantothenic acid  
Synthesized in 1940

**Inositol.** This occurs in almost all plant and animal tissue cells. Citrus fruits form a good source, also yeast. White mice on a deficient diet lose their hair and develop a dermatitis. The compound is water-soluble and sweet.



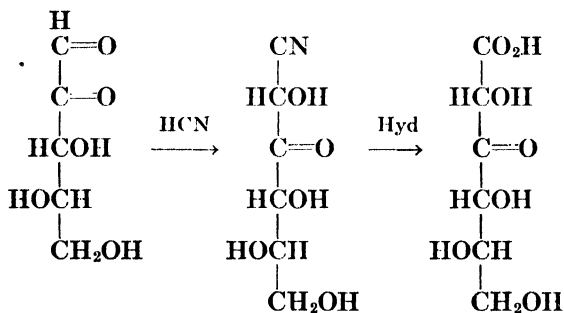
Inositol

***p*-Aminobenzoic Acid.** This vitamin may be isolated from yeast. Growth-promoting for chicks, prevents graying of fur in rats. A growth factor for many bacteria, e.g., *clostridium acetobutylicum* (page 790).

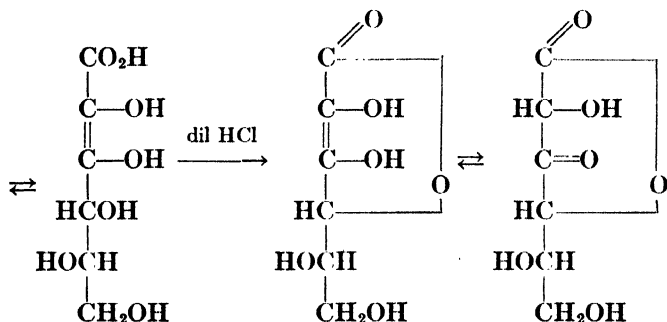
**Vitamin C. Ascorbic Acid.** Lack of vitamin C induces scurvy in men and guinea-pigs. The use of fruit juice to combat this condition has been known for about 200 years. C occurs in fresh fruits, notably orange and tomato, and in vegetables and red peppers; also in the adrenal cortex. C is water-soluble; is harmed by cooking operations when exposed to air. It is sensitive to alkali, stable towards weak acids. Adult requirement, 50–100 mg. Large doses of vitamin C were recommended (1942) for the relief of hay fever. Synthesis of ascorbic acid from L-xylosone is given below.



FIG. 104.—Bottle of synthetic vitamin; the equivalent of trainloads of rice polish. (*Ind. and Eng. Chemistry.*)



Vitamin C  
synthesis (1933)  
U. S. synthetic production (1940), 17 tons; 1943, 100 tons (estimated). Prices per ounce: 1933, \$213; 1942, \$1.65

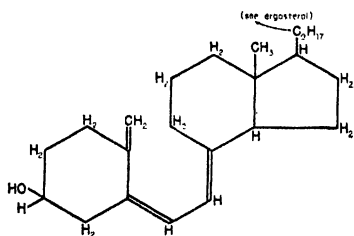


L-Ascorbic acid, Vitamin C. The D-acid is much less active.

**Vitamin D.** The D group contains a number of compounds, of which D<sub>2</sub> and D<sub>3</sub> are best known. The simple term "vitamin D" is usually applied

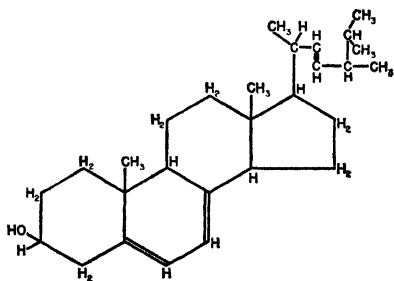
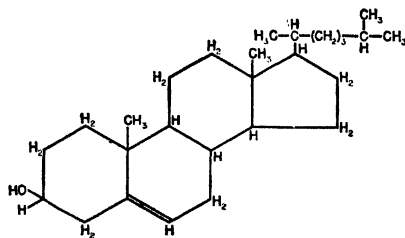


to the group. They are fat-soluble. D is intimately concerned with the deposition of bone salts; absence or deficiency is associated with the onset of rickets. In rickets there is a derangement of the calcium and/or phosphorus balance which interferes with proper bone growth, and in the growing child results in bow-legs and other malformations. The disease is cured by exposure to direct sunlight or ultraviolet light, or by the addition of vitamin D to the diet. The ultraviolet irradiation of foods having small vitamin D potency is also found to make them antirachitic. Evidently there is present both in the foods mentioned and in the human skin\* some substance which with ultraviolet illumination becomes antirachitic. One such substance upon isolation proved to be ergosterol, one of the class of sterols,† whose formula is given below. Ergosterol (a provitamin) is transformed by

Calciferol, Vitamin D<sub>2</sub>

Vitamin D<sub>3</sub> is identical save for the aliphatic side-chain which is  

$$\begin{array}{c} \text{H} \\ | \\ -\text{C}(\text{CH}_3)(\text{CH}_2)_3\text{CH}(\text{CH}_3)_2 \end{array}$$

Ergosterol  
Isolated 1811  
(Braconnot)

Cholesterol

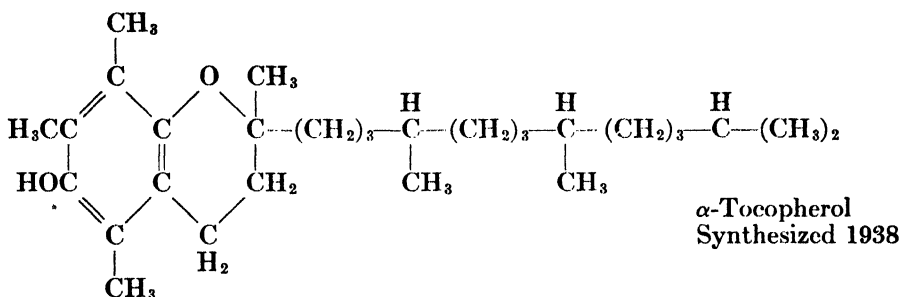
\* Experiments at Institutum Divi Thomae have shown that vitamin D and its precursors are removed from the surface of skin by ordinary washing. In the normal course of events the vitamin precursors in the skin secretions would be reabsorbed after irradiation. It has also been shown that rats can absorb sufficient vitamin A (from halibut-liver oil) through the skin to maintain healthy growth.

† The sterols are solid alcohols associated in nature with plant and animal fats. Cholesterol of the bile, the chief constituent of gallstones, is the best known. Stigmasterol, C<sub>29</sub>H<sub>47</sub>OH, one of the plant sterols (phytosterols) has been used as a starting material for the synthesis of progesterone.

illumination to vitamin D<sub>2</sub> (calciferol). Similarly 7-dehydrocholesterol is changed to D<sub>3</sub>.<sup>\*</sup>

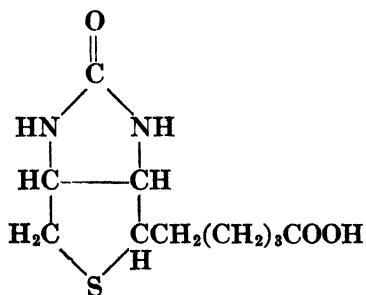
Sources of vitamin D are halibut- and cod-liver oil, egg-yolk, milk. The vitamin is fairly stable to oxidation and not harmed by cooking operations. Overdose of D causes excessive deposits of calcium to occur.

**Vitamin E.** The term "vitamin E" is applied to three tocopherols, two of which are isomers; the third is homologous to the others. In experiments with laboratory animals it has been demonstrated that both vitamins A and E must be present in the food if normal reproduction is to occur. However vitamin A has other functions, while for vitamin E the prevention of sterility is so far the best known function. Hence to this extent E may be called antisterility vitamin. It is a fat-soluble substance, found in milk, butter, green leaves, and in the germ oil of wheat or cottonseed. When omitted from the food of the test animals they gradually cease to produce their young.



The vitamin is stable to air, heat, and light, to a high degree. It also resists destruction by mineral acids and alkali. It is inactivated by rancidity of certain associated fats (lard, hydrogenated cottonseed oil).

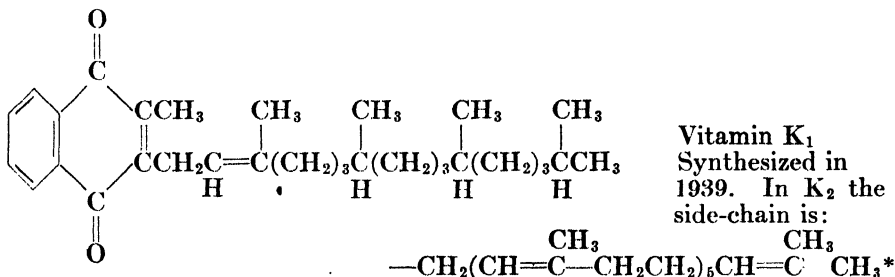
**Vitamin H, Biotin.** This is widely distributed in plants and is present in most animal tissues. It is apparently needed by all animals. Rats deprived of H develop a dermatitis and other abnormal symptoms and finally die.



Biotin. Proposed formula of 1942  
(du Vigneaud) established by synthesis of the compound (1943)

\* The following compounds are antirachitic after irradiation: 7-dehydrositosterol, 7-hydroxycholesterol, 22-dihydroergosterol. Irradiated crude cholesterol also is antirachitic.

**Vitamins K.**  $K_1$  and  $K_2$  are known at present.  $K_1$  occurs in plants (cabbage, tomato), also in egg-yolk, liver.  $K_2$  is present in microorganisms.  $K_1$  and  $K_2$  are fat-soluble; they are needed for the normal coagulation of the blood.



A well balanced diet containing a reasonable amount of fresh fruits, fresh vegetables, and milk, insures that one will obtain a sufficient intake of vitamins, as but small amounts of each are essential to one's physical welfare. Attention to the diet is a matter of considerable importance especially for the growing child; although the shortage of any particular vitamin may not reach the point where a deficiency disease is noted, there is always the danger of lowered vitality, with a decreased resistance to infection. It may also be imagined that a faulty diet given a growing child might lead to certain irregularities in development, which, not perceptible at the time, would appear later in life.

In addition to the vitamins discussed here others have been reported from time to time, e.g., vitamins P,  $B_7$ , J,  $L_1$ ,  $L_2$ , M, T, U, etc.; also essential fat acids, amino acids (page 721), choline (page 314), betaine (page 246). Information relative to the nutritional significance of these compounds should be sought in special monographs (see page 755).

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\* 2-Methyl-1,4-naphthoquinone, in which the side-chain is H has higher activity than  $K_1$

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## CHAPTER XXXIX

# CHEMISTRY IN THE HUMAN BODY

## DIGESTION, ABSORPTION, AND METABOLISM

Man's food is generally divided into five classes: water, salts, proteins, carbohydrates, and fats.\* In this chapter we shall consider how the substances of the last three groups are made available for the needs of the body (digestion, absorption), and how they are finally broken down and eliminated (metabolism).

Digestion of fats, carbohydrates, and proteins is similar in that it consists of the breakdown of complex molecules into simple water-soluble units which can enter and circulate in the body fluids. The breakdown is in each case assisted by enzymes. It is highly probable that in the synthesis of various body tissues from the foodstuffs enzymes again play a part; thus the total number of participating enzymes is certainly very large, and there is no assurance that all of them are known.

**Carbohydrates.** It appears that neither starch nor the disaccharides can be effectively utilized by the body until they have been reduced to their most simple factors, the monosaccharides. Digestion begins in the mouth, where the enzyme ptyalin (salivary amylase) initiates the hydrolysis of starch to dextrins and maltose. This hydrolysis proceeds for some time in the stomach, but gradual increase of the hydrochloric acid concentration through contact with the stomach contents progressively inhibits the action of ptyalin, and there is no further digestion until the small intestine is reached. Here the medium is mildly alkaline, and amylopsin, an enzyme of the pancreatic juice, carries on the hydrolysis begun by ptyalin. Maltase, which is secreted by the small intestine, converts maltose to glucose, while sucrase and lactase convert cane sugar and lactose to their hydrolysis products, glucose and fructose for the former, glucose and galactose for the latter.

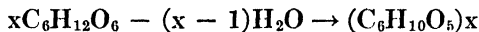
The absorption of the simple molecules obtained by the breaking down of the foodstuffs occurs principally in the small intestine, though a small amount of absorption has been noted in the stomach. The inner wall of the small intestine is thrown into numerous folds and possesses countless minute projections known as villi. These are especially numerous in the first few feet of the small intestine.

The individual villus has a central canal, known as a lacteal, through which materials can leave the intestine, and also an ample capillary system.

\* This list takes no account of any accessory factors, such as vitamins.

The blood vessels unite in the portal vein which leads to the liver. The lacteals unite in larger lymph vessels, finally leading to the thoracic duct. Material collecting in this system is added to the blood stream near the point where the left subclavian vein joins to the jugular vein.

The simple sugars formed by the hydrolysis of carbohydrates are taken into the blood stream by way of the capillaries of the villi and go by way of the portal vein to the liver. Here the excess of carbohydrate is stored in the form of glycogen,  $(C_6H_{10}O_5)_x$  often called "animal starch." The glycogen is evidently formed from glucose\* by a condensation with loss of water:



Its production by the liver is moderately rapid. The concentration of glucose in the blood is quite constant (about 0.09%) and is seldom over 0.15% except in cases of diabetes or in periods just following the ingestion of large amounts of sugar. When an excessive amount of sugar is found in the blood the condition is known as glycemia (hyperglycemia). Excess in the urine is called glycosuria. Normally the liver breaks down a sufficient amount of glycogen to keep the concentration constant. Glycogen is also formed and stored to some extent in the muscles and is freed from this source when needed for the production of energy. The muscle tissue forms from 40-45% of the body weight and the glycogen content possibly rises to about 1%, therefore for a normal adult the muscle glycogen may be about 300 grams.

The formation of glycogen in the liver is influenced by insulin (insulin inhibits the glycogen-glucose reaction). The formation of glucose from glycogen appears to depend upon an enzyme, glycogenase, which in its turn is activated by adrenaline. The regulating mechanism can be pictured as follows: excess blood sugar leads to secretion of insulin by the pancreas; this halts glucose formation in the liver. If the blood sugar becomes low the adrenals secrete adrenaline which stimulates the formation of glucose from liver glycogen.

So far, then, the changes suffered by carbohydrate foods in the body are: (1) hydrolysis to simple sugars (glucose, fructose, galactose); (2) conversion to glycogen (glycogenesis); (3) hydrolysis of glycogen to monosaccharide (glycogenolysis).

Ingested carbohydrate may be stored as glycogen or oxidized, or transformed to fat, or to some extent transformed to amino acids for protein manufacture. The metabolic rate rises during the digestion of food, this effect being known as specific dynamic action. The S.D.A. for carbohydrate is about 6%. The ultimate fate of the blood sugar, mainly glucose, is its

\* Fructose and galactose are changed to glycogen in the liver. Fructose forms glycogen more rapidly and to a greater extent than does glucose, galactose more slowly and to a very small extent (experiments with rats).

oxidation to carbon dioxide and water, which is productive of heat and other forms of energy. The oxidation is however preceded by a breaking down of the molecule whose exact nature is not perfectly clear.

During muscular contraction there is the production of lactic acid which is preceded by complex interchanges between hexose diphosphate, adenyl pyrophosphate, and glucose. The lactic acid is largely reconverted to glycogen, in part by muscle, in part by the liver, which then returns it to the muscle by way of blood glucose. A part of the lactic acid is oxidized to carbon dioxide and water. Some may escape in the urine. A vast amount of work has been done in connection with the oxidation of glucose and a coherent theory will probably be formed after further consideration of the accumulated data.

It seems to be fairly well established that the sequence of oxidation of glucose to final carbon dioxide and water, also the synthesis of fat from carbohydrates both demand an adequate supply of vitamin B<sub>1</sub>.

Glucuronic acid,  $\begin{array}{c} \text{OH} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{O} \end{array} \text{---} \begin{array}{c} \text{H} \\ \diagup \\ (\text{CHOH})_4\text{---} \\ \diagdown \end{array} \text{C=O}$ , an oxidation product of glu-

cose, is found in the blood and urine. The substance is of interest because when certain harmful substances such as camphor or phenol are found in the body, they are there combined with the glucuronic acid and then eliminated in the urine.

Certain portions of carbohydrate which escape digestion may undergo bacterial fermentation in the large intestine, producing a variety of aliphatic acids and other products, none of which is likely to be pronouncedly harmful.

**Fats.** The digestion of fats begins in the small intestine where, under the influence of the enzyme steapsin, a lipase of the pancreatic juice, which is activated and assisted by acids of the bile secretion, they are converted to fatty acids and glycerol. The bile salts, by lowering the surface tension, aid in emulsification. A small amount of soap formed at this time may perhaps assist in the emulsification of the unchanged fats and so cause their more ready hydrolysis(?). It should be noted that fats already emulsified may be digested in the stomach as well as in the intestine, lipase being present in both situations. The bile, pancreatic juice, and intestinal secretion are all alkaline. Their combined effect is to lower the acidity caused by the acid of the gastric juice.

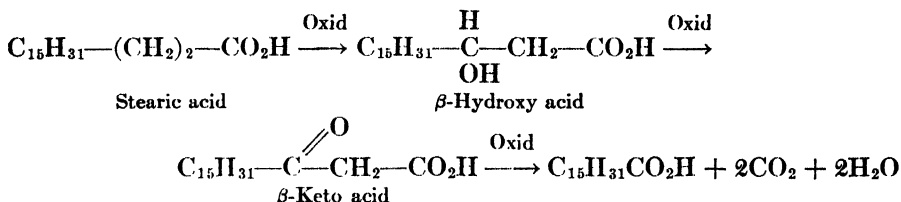
Fatty acids and glycerol are absorbed in the small intestine, mostly by way of the lacteals of the villi, and are apparently very soon resynthesized to fat, which then enters the venous circulation by way of the thoracic duct. In this resynthesis of fats those molecules which are characteristic to the body would naturally be formed; hence the process of splitting and synthesis would serve a real purpose.



It is possible that lipase assists in the synthesis of fats in the body as well as in their degradation. Certainly this reversibility has been observed in laboratory experiments with lipase (see page 738). Again, it seems highly significant that an esterase is found in the blood, the liver, in muscles, etc. It is possible that fat is split and remade more than once in the course of its service in the body.\*

The fat taken into the circulation may be used (1) in the synthesis of more complex substances of the body; (2) it may be stored in adipose tissue for future use;† (3) the glycerol fraction may be changed to glucose; (4) it may be utilized for energy. In the latter event the fat is oxidized to carbon dioxide and water, probably after a preliminary hydrolysis to glycerol and fatty acids. The exact mechanism of oxidation is not known. The glycerol is presumed to follow the same course as a carbohydrate. With regard to the fatty acids, one theory (that of Knoop) is that oxidation takes place on the *beta* carbon atom, giving first a hydroxy acid, then a keto acid. This on further oxidation loses two carbons as acetic acid (ultimately as carbon dioxide and water).

In the following equations stearic acid is used as an example:



As the acids of natural fats have an even number of carbon atoms, the type of degradation pictured above would finally lead to butyric acid derivatives. Actually, in diabetes and in fever conditions, we observe the "acetone bodies," *beta*-hydroxybutyric acid, acetoacetic acid, and acetone, in the urine. Acetoacetic acid could well have been formed by the oxidation of *beta*-hydroxybutyric acid, to later yield acetone as a decomposition product (see page 211).

Conditions which cause faulty carbohydrate metabolism are apparently responsible for the failure in fat metabolism which leads to the production of the acetone bodies.

Fat is a very highly concentrated food. About 90% or more by weight is suitable for energy production, and the calorific value is 9 large calories per gram. The S.D.A. is about 4%.

**Proteins.** Proteins begin the cycle of digestion in the stomach under the influence of pepsin. The stomach contents normally contain hydrochloric

\* Since esterase acts only very slowly upon fat glycerides, and the presence of enzymes with fat-splitting power has not been demonstrated in tissue cells, this is only a hypothesis.

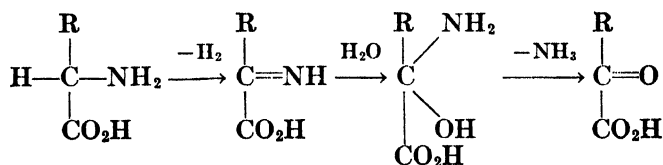
† It has been found in studies with rats that stored fat is constantly being exchanged. About half of the storage fat of the test animals was replaced in from five to nine days.

ric acid in a concentration of about 0.25–0.5%. Pepsin in this acid medium induces the hydrolysis of proteins to proteoses and peptones. Another enzyme, rennin, in combination with calcium ion, causes the coagulation of casein of milk to calcium paracaseinate. In this way milk when ingested is retained in the stomach for a longer time than if it remained in liquid form. In the small intestine the digestion is carried forward by the enzymes trypsin, aminopolypeptidase, dipeptidase, and carboxypolypeptidase.

Apparently the amino acids formed by the hydrolysis of protein food are absorbed by the blood system of the villi without further change and are carried to the various tissues, there to be synthesized into the different complex proteins characteristic of the individual organ. The final metabolism of fats and of carbohydrates is of course very complex and has not been cleared up in all details. With the proteins additional complexity is introduced through the necessity of considering so many different amino acids; this will not be attempted here.

The amino acids may be used for tissue synthesis or repair, for the making of specific compounds such as hormones, or for energy production. By deamination an amino acid may be converted to a keto acid; presumably this is the first step in the transformation to glucose which occurs with a number of the protein amino acids.

#### *Deamination.*



As some amino acids can form glucose and glucose can form fat, there is here an indirect path from protein to fat. The ammonia coming from the deamination is nearly all converted to urea in the liver and voided as such in the urine.

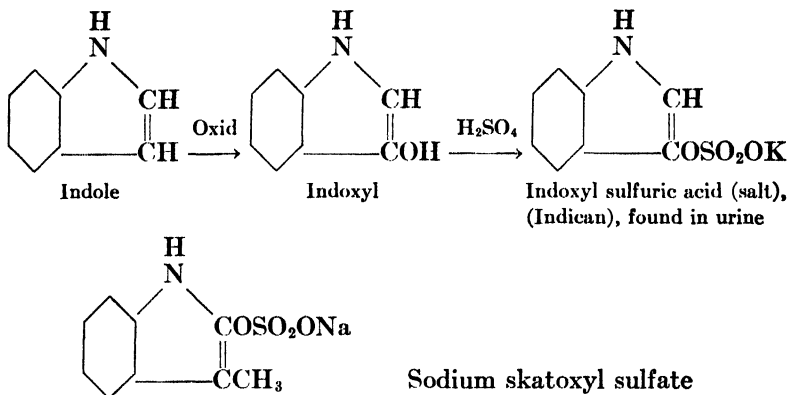
**Nitrogen Balance.** Unless the body is gaining weight through growth or wasting away by reason of disease, the nitrogen excretion is on a level with the nitrogen intake.\* The necessary protein intake to make up for bodily “wear and tear” is quite small, possibly 30–40 g. a day. Normally an adult eats more than this amount. The body can synthesize some amino acids by a reversal of the deamination process shown above, but in case of protein starvation this would not be of help, since the indispensable amino acids would be lacking. Protein has a higher specific dynamic action (30%) than either fat or carbohydrate. The S.D.A. of a mixed diet is about 10%.

**Detoxication.** Protein matter which escapes digestion in the small intestine normally undergoes bacterial putrefactive changes in the large intestine.

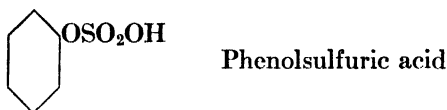
\* It is possible that the liver maintains a small amount of protein deposit (as amino acids).

tine. A great number of substances, some of which are toxic in their nature, are formed as a result of the complete breakdown which takes place during this action. Among these are indole, skatole, phenol, phenylacetic and phenylpropionic acids, carbon dioxide, hydrogen sulfide, methane, ammonia, hydrogen, and other compounds.

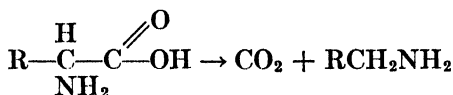
Indole and skatole are absorbed by the intestine and later eliminated in part in the urine, after being oxidized to indoxyl and skatoxyl respectively, and combined with sulfuric acid:



Phenol and cresol are eliminated in the urine partly free, partly conjugated with sulfuric acid:



It seems evident that indole and skatole arise from tryptophan, while phenol and cresol proceed from the degradation of tyrosine, and benzoic acid from phenylalanine. By a loss of carbon dioxide, similar in effect to the Hofmann reaction, amino acids may form amines:



In this way, substances like cadaverine (page 315), indoleethylamine, etc., may be formed by bacterial action upon protein amino acids.

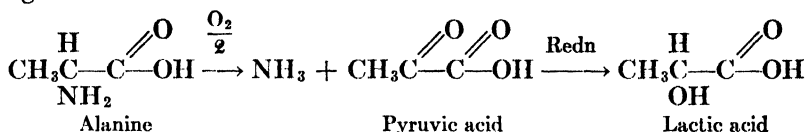
#### INTERCHANGEABILITY OF FOODSTUFFS (RÉSUMÉ)

The available heat energy of the three classes of foodstuffs has been calculated to be:

For protein,	1 gram = 4000 calories
For fat,	1 gram = 9000 calories
For carbohydrate,	1 gram = 4000 calories

Fats are seen to produce more energy when oxidized than do either carbohydrates or proteins. This is in accord with the make-up of the three types of molecules. Carbohydrates contain a relatively high percentage of oxygen (in  $C_6H_{10}O_5$ ,  $O = 49\%$ ). Proteins, again, have relatively much less carbon than fats ( $C =$  about  $50\%$  for proteins, but over  $70\%$  for fats). Thus, the fats, which have a higher carbon percentage than the proteins, and are less oxidized than either carbohydrates or proteins, should furnish more heat when burned.

Under certain conditions, perhaps by the influence of specific enzymes, proteins may be converted to carbohydrate in the body. Thus, alanine by deaminization is changed to lactic acid, from which the body can form glycogen:



As evidence that the body can change protein material to sugar, we have the experience of diabetic dogs, which, although fasting, continued to excrete sugar in the urine. About  $58\%$  of protein may be converted to carbohydrate.

There is no evidence that sugars can be formed in the body from higher fatty acids, but it appears that glycerol can be transformed to glycogen. To this extent, then, fats may be changed to sugars. It is also believed that fats may be synthesized in the body from the deaminized acids of the protein molecules (see page 761). The production of fat from carbohydrate in the body is a well known fact.

### PHYSIOLOGICAL ACTION OF DRUGS

In the preceding paragraphs, the changes which the various foodstuffs undergo during digestion and utilization by the body were briefly described. We shall now discuss, with considerable brevity, the same topics as related to drugs. The physiological effects of various simple organic groupings belong to this discussion, but it will be necessary to omit all consideration of the theories concerning the action of drugs on the human organism.

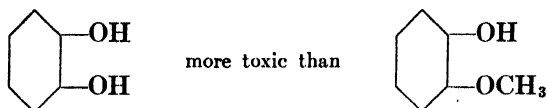
Organic compounds serve admirably in a study of the effect of structure upon physiological action, since it is possible to prepare derivatives in series which vary regularly one from another in physical properties, or which carry a certain group in a variety of placements. Studies of this nature have shown that there is a strong connection between the constitution of a compound and its physiological action. A slight alteration in the position of a group may entirely change the mode of action of a drug.\* Often *d*- and

\* *L*-Nicotine is more toxic than the *d*-isomer. The *antioxime* of perilla aldehyde is reputed to be 2000 times as sweet as sucrose; the *synoxime* is not sweet. *p*-Ethoxyphenyl urea (dulcin) is sweet, but the *ortho* isomer is **tasteless**.

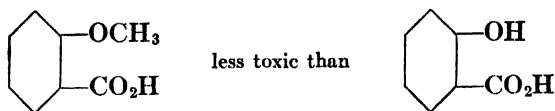
*l*-isomers have quite different effects. Such matters as solubility, volatility, molecular weight, etc., also have a bearing on the action of drugs. The influence of these various factors will be brought into the following discussion.

#### EFFECTS OF SOME IMPORTANT GROUPS

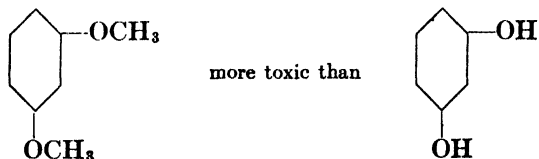
**Hydrocarbons and Alkyl Groups.** The aliphatic hydrocarbons have a narcotic action. The lower members produce sleep upon inhalation, and higher members are more toxic and narcotic. This action finally becomes less as solubility and volatility diminish. Thus, the solids are harmless. Olefins have a greater narcotic effect (see page 60). Benzene has a depressing influence upon the brain and a paralyzing effect upon the motor nerves. Naphthalene is more toxic than benzene. Alkyl groups in many cases cause a decrease in toxicity when substituted for hydrogen; however, in some instances, the effect is to the contrary. Thus, catechol is more toxic than guaiacol:



and *o*-methoxybenzoic acid is less toxic than salicylic acid:



however, resorcinol dimethyl ether is more toxic than resorcinol:



Toluene is more toxic than benzene; the xylenes are less toxic.

**Halogens.** The entrance of chlorine into aliphatic compounds usually increases their narcotic action, the amount of increase depending upon the halogen content. This is well shown in the series,  $\text{CH}_3\text{Cl}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $\text{CHCl}_3$ ,  $\text{CCl}_4$ , where toxicity increases along with increased narcotic action. In some cases, increase of chlorine content decreases the toxicity of aliphatic compounds. This is the rule with the sodium salts of the chlorinated acetic acids. In aromatic compounds, the properties are not greatly changed by introduction of chlorine; toxicity is increased. As we go from chlorine to iodine, narcotic action lessens and antiseptic action becomes more marked.

**Hydroxyl Group.** The introduction of successive hydroxyl groups into aliphatic compounds lessens their toxicity. Monohydroxy alcohols are

HENRY GILMAN. (American, 1893- .)

Gilman's work has been divided between synthesis and the study of reaction mechanism. He has researched particularly with organometallic compounds (Grignard reactions) and with furan derivatives and free radicals. He is editor of the recent advanced treatise of organic chemistry. Now professor of organic chemistry in Iowa State College.



MORRIS S. KHARASCH. (American, 1895-

.) Theoretical and synthetic work with organic mercurials, ethylene compounds. Heats of combustion of organic compounds, and relationship of electronic structure to physical properties of organic compounds, Grignard reactions, the peroxide effect. Now professor of organic chemistry in the University of Chicago. See pages 69, 117.

narcotic and toxic, whereas the polyhydroxy alcohols are harmless, and their derivatives, the sugars, serve as useful foods. In aromatic compounds, the OH group brings toxicity and antiseptic powers to the compound. Toxicity increases with an increase in the number of hydroxyl groups introduced.

**Acid Groups.** Acid groups cause a decrease of toxicity in their compounds. Several examples have been cited in the sections dealing with the breakdown of foods. Thus, phenol and cresol are transformed by the body to their sulfuric acid derivatives which are much less toxic. The same is the case with skatole and indole. Carboxyl group and sulfo group in organic compounds lessen toxicity. Benzoic acid is less toxic than benzene, while salicylic acid has a lower toxicity than phenol. In saccharin, we have both carboxyl and sulfo groups. The compound is harmless in spite of its possession of "ammonia nitrogen," which, in general, has toxic effects. Acyl groups often exert a like effect, e.g., aniline is more poisonous than acetanilide.

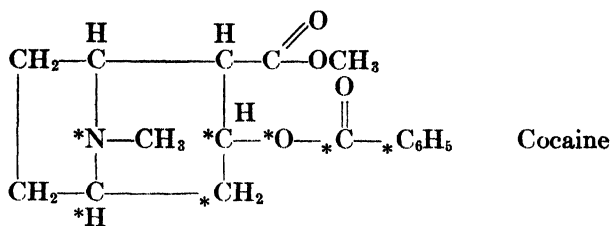
**Inorganic Groups.** With inorganic salts, the physiological effect appears to be due almost entirely to the positive ion. The effect is dependent upon the nature of the ion, and the solubility and per cent of ionization of the salt. Salts of zinc, iron, and aluminum have astringent properties, the first named having also an antiseptic action. Silver and mercury compounds have antiseptic power. Arsenic and antimony compounds have already received mention (page 602).

#### ALTERATION OF DRUGS IN THE BODY

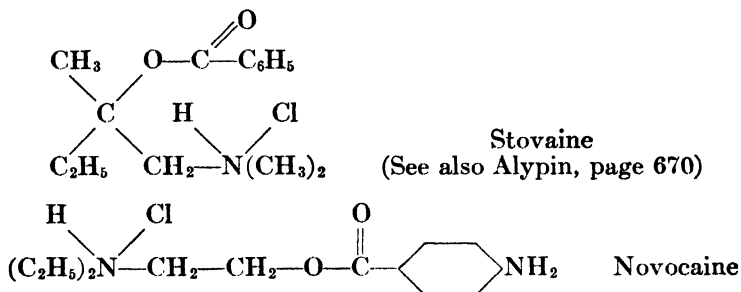
The majority of drugs are so handled in the body as to convert active substances into others less active and less toxic. Usually, the latter are more acid in nature than their precursors. Hydrolysis, oxidation, and reduction reactions are carried out in the body in making these changes in toxicity, also syntheses. Among the latter are union with sulfuric acid or glucuronic acid, already mentioned. Aminoacetic acid is used similarly to render substances less toxic. By a study of the form in which a given drug is eliminated from the body, it is frequently possible to make changes in the molecular structure which increase greatly the value of the compound as a curative agent.

#### SIMPLIFICATION OF DRUGS

As the beneficial physiological action of certain complex drugs appears to reside chiefly in characteristic groups, which represent only a part of the molecule, there are a number of cases in which it seems preferable to synthesize new substances containing this particular group, rather than to synthesize the entire complex. An example is found in the case of cocaine:



The grouping indicated by asterisks, i.e.,  $\text{R}-\text{N}-\text{C}-\text{C}-\text{C}-\text{O}-\text{C}(=\text{O})-\text{R}$  is closely imitated in the following compounds which possess anesthetic action.



The material in this section, while admittedly fragmentary, is sufficient to show that in the synthesis of drugs, there are distinct guiding principles. The author hopes also that the intensely interesting nature of this type of chemical research has been, at least in part, revealed. Research in this field has recently been aided by the use of a transparent crustacean, *Daphnia magna*, as a test animal. This has made possible a direct inspection of the action of various drugs upon the internal organs. Much valuable information has been gained in this way bearing on convulsive effects upon muscle, anesthetic effects, staining of organs and tissues, and other biological responses.

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- See also list of biochemistry texts, p. 798.

## CHAPTER XL

### IDENTIFICATION OF ORGANIC COMPOUNDS

In order to identify and name an unknown organic compound, one may pursue two different courses: (1) perform a quantitative analysis and a molecular weight determination to fix the molecular formula of the compound; then, by a study of its reactions, assign it to its proper group. As an illustration of this method, suppose the formula secured was  $C_2H_6O$  and the compound proved to be an alcohol, then it could be ethyl alcohol and nothing else. This method is quite tedious and time-consuming, due to the difficulties which usually attend the quantitative analysis of organic compounds.

If (2) this compound were proved to be an alcohol by a study of its reactions, then its boiling point, specific gravity, etc., would tentatively identify it as ethyl alcohol. Now, if several derivatives were prepared from the compound and these agreed in melting and boiling points with values tabulated in the chemical literature for the corresponding derivatives of ethyl alcohol, the identification would be just as certain as by method (1), and the expenditure of time and effort much less. For this reason, the latter method is preferred by chemists when simple compounds are to be identified. It is likely that such compounds, together with their derivatives, will be described in the literature.

For the identification of new substances, that is those not already listed in the literature, every available item of information must be secured. It should be noted that for many substances which have been studied for years the structures have still to be worked out. The task of identification is never a simple one, but it is obviously less difficult to identify a compound already fully described than to fix the structure of a complex unknown molecule. Many of the specific "group tests" proposed here would, however, have value in working with the unknown. The information gained by such group tests would be a necessary supplement to that given by the quantitative analysis and molecular weight determination.

#### ANALYSIS AND IDENTIFICATION

(1) The compound must be pure. Mixtures are separated by the processes of distillation, crystallization, use of selective solvents, etc., a full description of which may be found in laboratory manuals of organic chemistry.

(2) The melting point, boiling point, density, refractive index, and other physical constants are of great assistance in an identification. Often, these are secured incidentally during the process of purification of the compound. The first three have the greatest importance, and frequently they are the only data recorded in the literature for a compound.

(3) The color, odor, taste, crystal form, etc., of a compound will aid one in making an identification. However, as taste and odor are somewhat matters of individual judgment, too much dependence should not be placed upon these properties.

(4) The compound is subjected to qualitative analysis (see page 8) to determine what elements it contains. If no test for oxygen has been made its presence must always be suspected. By the use of lists of compounds like those on page 804, "Derivation of organic compounds," one finds in what series the unknown compound should be sought. For instance, if only C, H, and Cl were found, the C, H, Cl, and C, H, O, Cl lists alone would need consideration, i.e., the compound could not be a urea derivative or an amine.

(5) The solubility of the substance in certain "key" solvents is ascertained. The information gained is of the greatest value in assigning the compound to its proper class. The solvents are: water, ether, sodium hydroxide solution, sodium bicarbonate solution, hydrochloric acid, concentrated sulfuric acid, 85% phosphoric acid. The use of these solvents permits the separation of organic compounds into nine solubility groups and the behavior of the unknown towards the key solvents places it in only one or perhaps two of these groups, thus narrowing the scope of the investigation.

Having fixed on one or two homologous series to which the compound may belong, one now makes specific tests for the particular functions concerned.

(6) A consideration of the physical properties of the substance, of the elements which it contains, and of its solubility behavior, allows one to eliminate a number of series at the outset. The solubility tests usually narrow the choice rather promptly to one, two, or perhaps three chemical series. More specific tests, coupled with reference to the literature, will then allow one to fix on the proper series to which the compound belongs and will finally indicate the identity of the unknown compound.

(7) When this point is reached, one or two derivatives are prepared whose physical constants must agree with those quoted in the literature for the suspected compound, before the identification may be considered complete.

(8) *Mixed Melting Point Determination.* In some cases one has on hand an authentic sample of a compound which is supposed to be identical with the unknown being investigated. If the material is a solid a mixed melting point determination may be made. For example it may be thought that the unknown is salicylic acid. If a known sample of pure salicylic acid

is available, equal portions of known and unknown are mixed for a melting point determination. For a positive identification the known compound, unknown compound, and mixture should all melt in the same manner and at the same temperature. The theory is discussed in the laboratory manual and in physical chemistry texts.

(9) In the following paragraphs are presented some of the outstanding properties and reactions which will be useful in the identification of several important series of compounds. This material is supplementary to the text, and in each case reference should be made to the body of the text for the equations of the various reactions, the explanatory matter concerning them and the physical properties of the compounds.\* Used in this way, the summaries should serve as a rapid review of the behavior of these compounds. It is not feasible for us to present in full the different laboratory procedures used by the analyst. Those intending to carry on the analysis and identification of organic compounds are referred to laboratory manuals of organic qualitative analysis for detailed descriptions of the actual technique employed in the various tests, and for the special tests which may be found necessary.

## C AND H COMPOUNDS

**Saturated Aliphatic Hydrocarbons.** Hydrocarbons are lighter than water, and insoluble in same. Those of this series do not react with nitric acid;† they react slowly with bromine, liberating hydrogen bromide. A solution of bromine in carbon tetrachloride may be used. Hydrogen bromide is insoluble in this medium, and if any is evolved it may easily be detected. Hydrocarbons are moderately soluble in alcohol, soluble in benzene, insoluble in concentrated sulfuric acid.

*Derivatives.* No suitable derivatives can be offered. This means that the specimen must be very carefully purified in order that its boiling point, refractive index, and density may be determined with considerable accuracy for comparison with the literature.

**Unsaturated Aliphatic Hydrocarbons.** These add bromine; when treated with a solution of bromine in carbon tetrachloride, the color is discharged without the evolution of hydrogen bromide. They are oxidized by a solution of potassium permanganate.

A dilute solution of potassium permanganate (Baeyer's reagent) is employed. The discharge of the purple color, and precipitation of brown manganese dioxide, are signs of reaction.

Unsaturated compounds generally break at the double or triple bond when oxidized. A study of the products of oxidation is often helpful in

\* For physical properties see also the table, page 808.

† Tertiary carbon atoms are subject to attack by nitric acid and by strong sulfuric acid, also by certain oxidizing agents.

identification. Compounds with the  $\equiv\text{CH}$  group form metallic derivatives. When treated with an ammoniacal solution of cuprous chloride, a dark-colored precipitate of a copper salt is produced. Unsaturated hydrocarbons are soluble in cold concentrated sulfuric acid (see page 71).

*Derivatives.* For the olefins the identification will probably rest upon a careful determination of physical constants. Acetylenic compounds form mercury salts which are suitable derivatives for their identification. With conjugated dienes the Diels-Alder reaction with maleic anhydride or other suitable compound may be used to obtain a solid derivative.

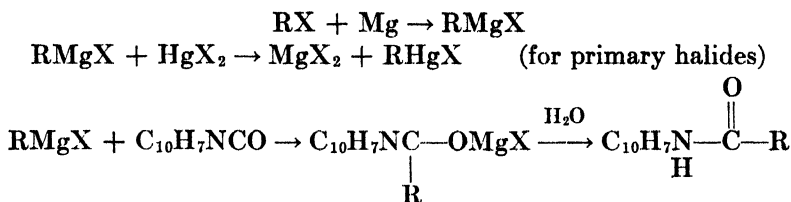
**Aromatic Hydrocarbons.** These dissolve, with or without the application of heat, in fuming sulfuric acid. Simple aromatic hydrocarbons do not dissolve in cold concentrated sulfuric acid. Treated with nitric acid they give nitro compounds heavier than water. Those with alkyl side-chains may perhaps be oxidized by nitric acid to give aldehydes or acids. Hydrocarbons with several rings (condensed) often form molecular compounds with picric acid which have definite melting points. Aromatic hydrocarbons dissolve in dimethyl sulfate, and they participate in the Friedel-Crafts reaction. The aliphatic saturated hydrocarbons are insoluble in dimethyl sulfate, do not take part in the Friedel-Crafts reaction.

*Derivatives.* Nitro compounds are very useful, also picrates. The oxidation of compounds with side-chains with permanganate solution gives solid acids.

## C, H, AND CL COMPOUNDS

**Alkyl Halides.** These are practically insoluble in water and in concentrated sulfuric acid, and ionize but slightly. Chlorides are lighter than water, while bromides and iodides are heavier. Compounds with several halogen atoms have high densities. The iodides show greater activity in general than the bromides or chlorides. Lower members have a peculiar sweetish odor. They give the Beilstein test, that is, when heated on a copper wire in the Bunsen flame, a green or violet color is produced. Alcoholic potash converts them to olefins, and aqueous alkali causes hydrolysis, with the production of the corresponding alcohols. In either case, a precipitate of silver halide is secured when the resulting solution is made acid with nitric acid, and treated with silver nitrate solution. They react with sodium to give hydrocarbons (Wurtz reaction), and combine with ammonia to form ammonium salts. With metal salts, they react by double decomposition (page 82).

*Derivatives.* There are several derivatives among which to choose. A good method involves (1) preparation of a Grignard compound (2) reaction of the Grignard compound with a mercuric halide (for identification of primary halides) or with naphthyl isocyanate.



**Aryl Halides** are insoluble in water and in concentrated sulfuric acid. Their odors are faint but not unpleasant. They are not subject to hydrolysis (see exception, page 433). They react with sodium in the Fittig synthesis (page 432) and with magnesium in the Grignard reaction (page 432). Aryl compounds with halogen in the side-chain act like alkyl halides (page 433). In addition, these substances have a sharp piercing odor, and are lacrymatory (cause flow of tears).

*Derivatives.* These compounds may usually be nitrated. If there is a side-chain the oxidation to a halogenated acid may be in order.

**Acyl Halides.** These compounds have a characteristic piercing odor. The lower members fume in the air, due to the formation of halogen acid. They react with cold water to give a solution of organic acid and halogen acid. Amides, esters, and anilides are formed with ease.

**Aromatic Acid Halides.** These react but slowly with water, and are insoluble. Esters are formed by the Schotten-Baumann reaction (page 524).

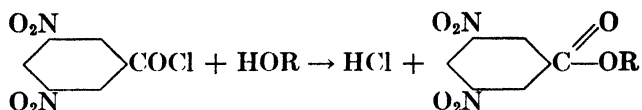
*Derivatives.* These compounds very easily give derivatives with ammonia and amines. Amides and anilides are solids, hence useful for identification purposes. Esters, if solid, may also be made. In some cases the hydrolysis of a halide to its acid may serve the purpose (when the acid is a solid).

## C, H, AND O COMPOUNDS

**Aliphatic Alcohols.** Hydroxyl group in most compounds will react (1) with sodium to liberate hydrogen; (2) with phosphorus halides to replace OH by Cl; (3) with an organic acid (anhydride, acid halide) to form an ester. Lower members of the alcohol series are water-soluble, as are all polyhydroxy compounds. With acid halides esters are formed. Lower members form solid esters of definite melting point with 3,5-dinitrobenzoyl chloride. Esters of polyhydroxy alcohols are made by the Schotten-Baumann method. Primary, secondary, and tertiary alcohols are distinguished by their oxidation products, but more readily by various comparative tests which have been worked out for the use of such reagents as phthalic anhydride, hydrobromic acid, HCl-zinc chloride, etc. These are described in the qualitative analysis text.

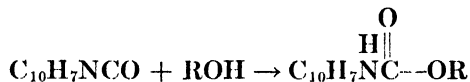
*Derivatives.* Many are known.

(a) Solid esters of 3,5-dinitrobenzoyl chloride:



(b) Esters of 3-nitrophthalic acid.

(c)  $\alpha$ -Naphthylurethans:

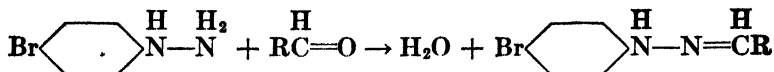


Phenyl isocyanate may be used in a similar way.

Tertiary alcohols are apt to react anomalously with ester-forming reagents and require special handling. Ordinarily they are identified by the use of their physical constants.

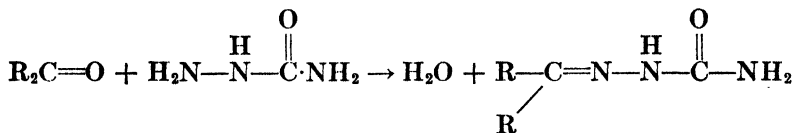
**Aldehydes and Ketones.** Formaldehyde has a sharp suffocating odor. The odors of the lower aldehydes are peculiar and characteristic. Some aldehydes and ketones form solid bisulfite compounds when shaken with a saturated solution of sodium bisulfite. Derivatives are formed with hydroxylamine and phenylhydrazine. Aldehydes affect Schiff's reagent (page 141) and are oxidized to acids when treated with nitric acid, etc. They reduce Fehling's solution\* or ammoniacal silver nitrate solution, giving a precipitate of cuprous oxide or metallic silver respectively. With strong sodium hydroxide solution, the aliphatic aldehydes, save formaldehyde, yield resinous compounds, while the aromatic aldehydes undergo the Cannizzaro reaction (page 491). Bromine in carbon tetrachloride solution reacts with aromatic aldehydes to form acid bromides (page 523). Ketones do not reduce Fehling's solution nor ammoniacal silver nitrate.\* They do not respond to the Schiff test. In ketones having a methyl group attached to the carbonyl, treatment with a solution of sodium nitroprusside and a little alkali develops a strong coloration (acetone gives a red solution), which is altered by the addition of acetic acid. Some aldehydes and ketones give the haloform reaction (page 144).

*Derivatives.* The phenylhydrazones of some aldehydes and ketones are solids and answer the purpose for derivatives. Substances that yield liquid phenylhydrazones may be treated with *p*-bromo- or 2,4-dinitrophenylhydrazine to obtain a solid derivative:

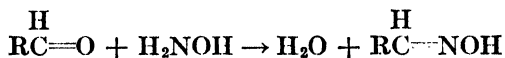


\* *Alpha*-hydroxy ketones, such as fructose, readily reduce Fehling's solution.

The semicarbazones, made with semicarbazide, may be used as well:



In some cases the formation of the oxime may be advantageous:



Derivatives for identification of specific aldehydes and ketones have been suggested in the body of the text at the appropriate places.

**Ethers.** Ethers are insoluble in water. Aliphatic ethers dissolve in cold concentrated sulfuric acid and may be recovered by pouring the resulting solution into ice-water. Treatment with hydrogen iodide yields alkyl halides. The aromatic-aliphatic ethers, when warmed with aluminum chloride, yield phenols and alkyl chlorides.

**Derivatives.** Aromatic ethers may be brominated or nitrated to give suitable derivatives. For aliphatic ethers there is no simple method of identification through preparation of a derivative.

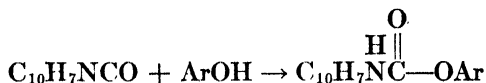
**Esters.** Esters are insoluble or very slightly soluble in water; they are soluble in cold concentrated sulfuric acid. They possess agreeable odors for the most part. When warmed with sodium hydroxide solution, they are hydrolyzed; concentrated hydrochloric acid may also be used for hydrolysis. The hydrolysis is usually performed in a quantitative manner in order to secure the *saponification equivalent* (the weight of ester which requires a gram-equivalent weight of alkali in the hydrolysis). The products of hydrolysis are recovered and examined independently. Concentrated ammonium hydroxide solution reacts with esters to form amides.

**Phenols.** These are soluble in sodium hydroxide solution, and differ in this way from aliphatic alcohols. They are weakly acid, and form salts which are stable in water, but which are decomposed by carbonic acid. They often have characteristic odors. Addition of ferric chloride solution gives colors, which vary for the different compounds (see pages 499 and 514). Coloration with ferric chloride is also shown by other hydroxy compounds, therefore the findings of this test have only a relative value. Bromine-water with a phenol gives a precipitate of brominated phenol (page 499). Acid halides form esters with phenols. Phenols, when treated with a solution of potassium nitrite in concentrated sulfuric acid, yield strong colors (Liebermann test). Ordinary phenol gives, finally, a blue color. The same test serves to detect the nitroso group. Many phenols when heated with phthalic anhydride and sulfuric acid give phthaleins. These yield strong colors in presence of an excess of alkali.



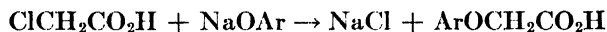
*Derivatives.*

(a) Urethans from  $\alpha$ -naphthyl isocyanate:



(b) Bromo derivatives, example, tribromophenol, page 499.

(c) Ethers of acetic acid:

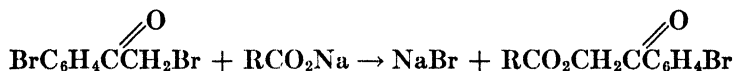


(d) Additional derivatives are: picrates, esters of 3,5-dinitrobenzoic acid, nitro compounds.

**Acids.** The lower aliphatic members only are water-soluble. Acids from butyric to capric have a foul odor. Aromatic acids are colorless solids, sparingly soluble in water. Hydrogen is liberated from the acids by the action of sodium, their solutions in water are acid to litmus, and bases form stable salts with them. They decompose carbonates giving carbon dioxide. The aliphatic monocarboxylic acids are oxidized or reduced only with great difficulty. Their dry sodium salts when heated with excess of strong base yield hydrocarbons. Esters form when the acids are warmed with excess of alcohol and concentrated sulfuric acid. The acid halide may be prepared from the acid by the use of phosphorus pentachloride, and in turn used to form esters or amides. Acids may be distinguished from phenols as their alkali salts are not decomposed by the action of carbon dioxide, while those of the phenols are. Ferric chloride reacts with aliphatic hydroxy acids to give a yellow coloration. The phenolic hydroxy acids, particularly the *ortho* acids, give blue or violet colors with this reagent.

*Derivatives. Aliphatic Acids.*

(a) Esters made with *p*-bromophenacyl bromide:



(b) Formation of the anilide or toluidide.

(c) Titration to obtain the neutralization equivalent of the acid. The neutralization equivalent is the weight of the acid (in grams) which will neutralize 1000 cc. of normal alkali. For a monocarboxylic acid it is the molecular weight, for a dicarboxylic acid it is half the molecular weight.

$$\text{Neutralization equivalent} = \frac{\text{Wt. of acid} \times 1000}{\text{cc. of alkali} \times \text{normality}}$$

*Aromatic Acids.*

Formation of amides and/or anilides and/or toluidides. A few generalizations can be offered for the dicarboxylic acids. All are solid, and several are unstable to heat or undergo reaction when heated (page 254). Analytical data are given on page 266 for hydroxy acids (tartaric and citric).

**Acid Anhydrides.** These compounds are very slightly soluble in water. They may be hydrolyzed with alkali to give salts of the acids. An ester also hydrolyzes with base to yield a salt, but in this case an alcohol is produced along with the salt (page 205). Esters and anilides, amides or toluidides may be formed from anhydrides as from acids. Aromatic anhydrides are solids, whose reactions resemble those of the aliphatic compounds.

**Glycosides and Carbohydrates.** These substances on strong heating develop characteristic burnt odors. They give the Molisch test (page 354). Treated with concentrated sulfuric acid, the glycosides exhibit strong colors. Glycosides respond to hydrolysis, after which the carbohydrate portion may be tested with Fehling's solution. The behavior of sugars and starch, etc., is given on page 352 and following pages.

**Derivatives.** For monosaccharides the osazones (diphenylhydrazones) may be used. For further data see Reference 7. For glycosides see Reference 8.

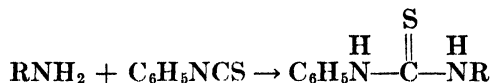
## C, H, AND N COMPOUNDS

**Aliphatic Amines** are basic to litmus and are soluble in acids, with which they form compounds by direct addition. They form precipitates with picric acid or platinic chloride solution. The primary, secondary, and tertiary amines are distinguished by their action with nitrous acid and by the Hinsberg reaction. The isocyanide test is useful to distinguish primary amines.

*Derivatives. Primary and Secondary Amines.*

(a) Benzenesulfonamides or similar type compounds such as  $\alpha$ -naphthylsulfonamides. (Equation, page 441.)

(b) Derivatives from phenyl mustard oil (phenylthioureas):



(c) Substituted amides from treatment with a suitable acid chloride or anhydride.

(d) Formation of picrates.

*Tertiary Amines.*

(a) Formation of picrates.

(b) Formation of ammonium salts with methyl iodide.

(c) Formation of salts with chloroplatinic acid.

**Aromatic Amines** are much less basic than the aliphatic. The primary amines may be diazotized; they form bromo derivatives when treated with bromine-water, and yield the isocyanide test. Primary, secondary, and tertiary compounds are distinguished by the use of the Hinsberg test. Primary and secondary amines react with acid halides to form substituted

amides. Primary amines after diazotization may be coupled with  $\beta$ -naphthol to give colored compounds (azo dyes).

*Derivatives* are as described for the aliphatic amines. In addition we have the *p*-nitroso compounds as derivatives for aromatic tertiary amines of the type of dimethylaniline.

**Azo Compounds.** These are in general highly colored stable solids. They reduce to amines with rupture of the  $\text{—N=N—}$  union (page 485), with consequent loss of color.

**Hydrazo Compounds** (aromatic) are colorless solids, which easily oxidize to colored azo compounds. Warmed with dilute acids they undergo the benzidine rearrangement (page 473). They may readily be reduced to amines. Like amines, they are subject to acylation, forming mono- and diacyl derivatives.

**Nitriles.** These are insoluble in water. Nitriles yield ammonia slowly when boiled with sodium hydroxide solution. If the hydrolysis yields a solid acid this may serve as a derivative, or it may be treated to form a suitable derivative. When heated with alcohol and concentrated sulfuric acid, oxygen esters are formed. Reduction gives primary amines. Partial hydration by gentle treatment with dilute alkali leads to the production of amides.

**Isocyanides** have disagreeable odors. They are hydrolyzed to produce formic acid and primary amines (page 287), and are easily oxidized to isocyanates by mercuric oxide, giving a precipitate of metallic mercury.

### C, H, N, AND O COMPOUNDS

**Amides.** These readily yield ammonia and an acid (salt) when warmed with alkali. Nitriles are formed by heating amides with phosphorus pentoxide. Through the Hofmann reaction, amides are transformed to lower amines.

*Derivatives.* The acid formed by hydrolysis is characterized in the usual way.

**Isocyanates** have irritating odors. They are extremely reactive, and may be identified by their action on substances containing OH or  $\text{NH}_2$  groups (page 290).

**Aromatic Nitro Compounds** may be reduced to amines in acid solution, or in alkaline solution to azoxy, azo compounds, etc. Those in which OH or  $\text{NH}_2$  is substituted are usually colored; the nitrophenols give highly colored solutions in alkali.

*Test for Nitro Group.* The compound is heated with zinc dust in dilute alcoholic solution of ammonium chloride. This reduces the nitro group to hydroxylamine group. The aryl hydroxylamine gives a silver deposit when treated with ammoniacal silver nitrate solution.

*Derivatives.*

(a) Polynitro compounds, made by further nitration.

(b) **Amines**, formed by complete reduction. These are identified in the usual way.

**Proteins.** Proteins, when heated alone, give a characteristic odor of burnt hair or feathers. Specific color and precipitation tests are given on page 723, etc.

**Alkaloids.** Alkaloids are precipitated from their solutions by the following "alkaloidal reagents"—tannic acid, iodine in potassium iodide solution, platinic chloride solution, phosphomolybdic acid, phosphotungstic acid, gallic acid. Many develop strong colors when treated with concentrated sulfuric acid alone; or with the acid and a trace of nitric acid, potassium dichromate, or ammonium molybdate. The color first produced often changes after a time; a consideration of the colors and changes produced by these reagents helps in the identification of an alkaloid.

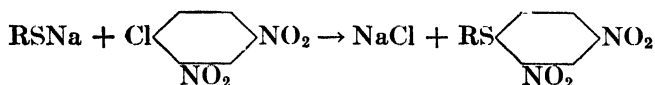
**Purines** generally give the murexide test. This consists in heating the substance with concentrated nitric acid, cooling, and adding ammonium hydroxide to alkaline reaction. A violet color results.

#### C, H, AND S COMPOUNDS

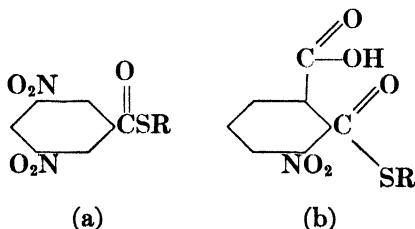
**Thioalcohols and Sulfides.** These possess foul, disgusting odors. Both classes may be oxidized, the thioalcohols to sulfonic acids, the sulfides first to sulfoxides, then to sulfones. Thioalcohols form salts as do alcohols (page 114).

*Derivatives of thioalcohols.*

(a) Preparation of thioethers with 2,4-dinitrochlorobenzene:



(b) Esters of (a) 3,5-dinitrobenzoyl chloride or (b) of 3-nitrophthalic acid:



#### C, H, S, AND O COMPOUNDS

**Aromatic Sulfonic Acids.** These are strong acids, quite soluble in water. When fused with excess alkali, phenols are formed. On treatment with phosphorus pentachloride acid chlorides result, which may be converted in the usual manner to esters or amides for complete identification.

For identification of aliphatic sulfonic acids, see *J. Am. Chem. Soc.*, **59**, 2500 (1937), also page 783.

### PROBLEMS

The properties of a number of compounds are listed in the following six problems. From a consideration of these properties assign each compound to one (or more) of the homologous series (hydrocarbon, alkyl halide, ether, etc.).

1. The compound contains C and H. It is lighter than water, and insoluble in same. Nitric acid reacts with it producing a yellow oil, insoluble in water.
2. The compound contains C, H, and O. It is slightly soluble in water, soluble in ether. A solution of the substance in dry ether when treated with sodium liberates hydrogen gas. The original compound reacts with acetyl chloride with liberation of hydrogen chloride.
3. The compound contains C, H, and Br. It is heavier than water and is insoluble. The odor of the compound is agreeable. It reacts with sodium giving a neutral substance containing C and H, but no halogen.
4. The compound contains C and H. It decolorizes bromine-water and reduces alkaline permanganate solution. Ammoniacal cuprous chloride solution is unaffected by the compound.
5. The compound contains C, H, and O. It dissolves somewhat in water and freely in sodium hydroxide solution. Ferric chloride solution gives a dark coloration. The compound reacts violently with concentrated nitric acid. It is insoluble in sodium carbonate solution.
6. The compound contains C, H, O, and N. When warmed with sodium hydroxide solution, ammonia gas is evolved. A characteristic piercing odor is observed when the compound is warmed with sulfuric acid.
7. What groups are suggested by the following tests?
  - (a) The compound contains C, H, and Br. When warmed with water it does not dissolve. The water layer gives a yellowish precipitate when treated with silver nitrate solution.
  - (b) The compound contains C, H, and S, has a bad odor. It is oxidized by nitric acid; it gives a heavy precipitate with lead acetate solution.
  - (c) The compound contains C, H, and O. It is a liquid of bad odor. It dissolves slightly in water; the solution reddens litmus paper. The neutralization equivalent is 88.
  - (d) The substance is an oil, very little soluble in water. It dissolves in dilute hydrochloric acid solution. When treated with hydrochloric acid and sodium nitrite in the cold, it gives a colorless solution. Addition of alkaline  $\beta$ -naphthol to this solution gives a red precipitate.
8. From a consideration of the following statements tell in each case the groups to which the unknown does *not* belong:
  - (a) C and H were found. The compound is a liquid, completely soluble in water.
  - (b) C and H were found. The compound burns with a smoky flame, is quickly oxidized by permanganate solution. It is a liquid. Sodium does not affect it.
  - (c) C, H, and N were found. The compound is a liquid. It gives ammonia when warmed with alkali.
  - (d) C and H were found. The compound, a solid, is unaffected by hot nitric acid.

### SPECIFIC IDENTIFICATIONS

1. A neutral water-soluble liquid organic compound contains the elements C, H, and O. It reacts with sodium, liberating hydrogen gas, and forming a solid derivative. This solid compound treated with ethyl iodide gives a liquid, very sparingly soluble in water, having a boiling point of  $34.5^\circ$ . What is the original compound?

2. A certain compound contains the elements C, H, and N. It is a liquid soluble in water. It reacts with acids, anhydrides, etc. The compound formed with acetyl chloride has the formula  $C_6H_{11}ON$ . Nitrous acid reacts with the compound, yielding nitrogen gas. Write the possible structural formulas for the original compound.
3. An organic liquid which contains C, H, and O has a characteristic odor, and is but sparingly soluble in water, giving a neutral solution. Warmed for some time with sodium hydroxide solution, the substance goes completely into solution. From this reaction mixture, a liquid is obtained, having a neutral reaction and a rather prominent but not disagreeable odor. Its boiling point is  $137.9^\circ$  and its acetyl derivative boils at  $147.6^\circ$ . Suggest to what class the original compound belongs, and the means necessary for its complete identification.
4. The substance butyric acid was given a student for identification. State in outline form the steps by which it was tentatively identified. What derivatives might be prepared for the complete identification of this substance?
5. A liquid of sharp unpleasant odor is completely soluble in water. It contains C, H, and O. Concentrated sodium hydroxide solution when warmed with the compound gives a reddish, gum-like precipitate. The compound easily reduces Fehling's solution and ammoniacal silver nitrate. To what class may the substance belong? What derivatives would you seek to prepare for the complete identification of the compound?
6. A certain solid, colorless hydrocarbon reacts well with sulfuric acid, nitric acid, or bromine. Its compound with picric acid has a melting point of  $150.5^\circ$ . What is the substance?
7. An organic hydrocarbon is easily acted upon by nitric or sulfuric acids. Its boiling point is  $110.5^\circ$ . Upon oxidation, a solid is produced whose melting point is  $121.7^\circ$ . This solid dissolves very sparingly in water (cold), but quite readily in sodium hydroxide solution. What is the original hydrocarbon?
8. A liquid of aromatic odor contains C, H, and O. It reduces ammoniacal silver nitrate solution and reacts with sodium bisulfite solution. The boiling point of the substance is  $179.5^\circ$ . With ammonia, a white solid is secured, whose melting point is  $101^\circ$ . Describe the further steps necessary for the identification of the compound.
9. A liquid of pleasant odor is practically insoluble in water; the solution is neutral. The substance is insoluble in sodium hydroxide solution, but after warming for some time it passes into solution. When this solution is acidified, a solid (A) whose melting point is  $121.7^\circ$ , is secured. The solid (A) reacts with phosphorus pentachloride giving a liquid product (B), of unpleasant odor. Compound (B) with aniline gives a solid, whose melting point is  $161^\circ$ . The sodium hydroxide solution also yields a liquid product (C), whose boiling point is  $78.5^\circ$ . The substance (C) is soluble in water, giving a neutral solution. It gives the iodoform test. Acetyl chloride reacts with (C), giving a liquid, whose boiling point is  $77.1^\circ$ . What is the original substance?
10. An organic liquid contains C, H, and O. Its odor is agreeable. The substance is insoluble in water, but dissolves in cold concentrated sulfuric acid, from which it is recovered upon treatment with ice-water. The boiling point is  $61.4^\circ$ . When distilled with hydriodic acid, two halogen compounds are formed whose boiling points are  $72.2^\circ$  and  $102.4^\circ$ , respectively. What is the original compound?
11. The compound, a white solid, melts at  $130-5^\circ C$ . with decomposition, liberating carbon dioxide. It is an acid with neutralization equivalent of  $52 \pm 1$ . Its decomposition product boils at  $118^\circ$  and has a neutralization equivalent of 60.
12. The compound is a colorless liquid, boiling point,  $154^\circ C$ . It is insoluble in water, soluble in ether, and in concentrated sulfuric acid. When heated with concentrated HI solution, compounds (A) and (B) are formed. Characteristics of (A): m.p.,  $42^\circ$ , colorless, soluble in water and in NaOH solution; gives purple color with  $FeCl_3$  solution; with bromine-water gives a solid, m.p.,  $95^\circ$ . Characteristics of (B): b.p.,  $42^\circ C$ .; gives Beilstein test; gives an  $\alpha$ -naphthalide of m.p.,  $160^\circ$ .

13. The compound (C, H, N) is a colorless gas of ammoniacal odor. It is soluble in water and in dilute HCl solution. It forms a picrate, yellow crystals, melting at 215°C. Phenyl isothiocyanate gives a derivative with m.p. of 113°C.
14. The compound (C, H) is a liquid with a pungent odor, b.p., 96°. It is soluble in water and in ether; it decolorizes bromine-water or KMnO<sub>4</sub> solution. The compound reacts with metallic sodium or with acetyl chloride; it does not respond to the iodoform test. Phenyl isocyanate gives a derivative with m.p. of 70°.

### REVIEW QUESTIONS

1. What analytical reactions are shared by phenols and aliphatic saturated primary alcohols?
2. How may an aliphatic ether be distinguished from an aliphatic saturated hydrocarbon?
3. By what sequence of tests would an ammonium salt of a saturated monocarboxylic acid be recognized?
4. A certain compound is known to have the formula C<sub>9</sub>H<sub>10</sub>O<sub>3</sub>. When oxidized it gives phthalic acid. Write all possible structures for the original compound.
5. Write equations showing the formation of the thioalcohol derivatives (a) and (b) on page 779 from 3,5-dinitrobenzoyl chloride and 3-nitrophthalic anhydride respectively.
6. Suggest suitable derivatives for use in the identification of the following compounds:
  - (a) Ethylbenzene.
  - (b) Benzamide.
  - (c) Butyraldehyde.
  - (d) Aniline.
  - (e) Methylamine.
7. What chemical and physical properties of the following compounds would be useful in finding for each its proper chemical series?
  - (a) Acetone.
  - (b) *o*-Toluidine.
  - (c) Hexane.
  - (d) Butyl ether.
  - (e) 2-Hexene.
8. A certain compound being analyzed reacted with sodium giving, evidently, hydrogen. The student thereupon concluded that it was an alcohol. What criticism can you offer?
9. State clearly how to distinguish each of the following compounds from the other compound listed. (a) Bromobenzene and *n*-hexyl bromide; (b) Aniline and phenol; (c) Benzoic acid and naphthalene; (d) Picric acid and phenol; (e) Acetamide and ammonium acetate; (f) Urea and succinimide; (g) Phthalic anhydride and cinnamic acid; (h) Paraldehyde and *n*-caproic aldehyde.
10. Give definite directions for the separation of the following mixtures. No substance is to be destroyed in the separation. (a) Nitrobenzene, aniline, ethyl ether; (b) Acetic acid, ethyl alcohol, ethyl acetate; (c) Aniline, ethylaniline, acetophenone; (d) Acetone, acetic acid, benzene, methyl alcohol; (e) Anisole, *o*-cresol, aniline.

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# ATOMIC WEIGHTS

(1943)

Aluminum.....	Al	26.97
Antimony.....	Sb	121.76
Arsenic.....	As	74.91
Barium.....	Ba	137.36
Boron.....	B	10.82
Bromine.....	Br	79.916
Calcium.....	Ca	40.08
Carbon.....	C	12.010
Chlorine.....	Cl	35.457
Chromium.....	Cr	52.01
Copper.....	Cu	63.57
Fluorine.....	F	19.00
Hydrogen.....	H	1.0080
Iodine.....	I	126.92
Iron.....	Fe	55.85
Lead.....	Pb	207.21
Magnesium.....	Mg	24.32
Manganese.....	Mn	54.93
Mercury.....	Hg	200.61
Nickel.....	Ni	58.69
Nitrogen.....	N	14.008
Oxygen.....	O	16.0000
Phosphorus.....	P	30.98
Potassium.....	K	39.096
Silver.....	Ag	107.880
Sodium.....	Na	22.997
Sulfur.....	S	32.06
Tin.....	Sn	118.70
Zinc.....	Zn	65.38

## FLOW SHEETS OF INDUSTRIAL SYNTHESSES\*

On the following pages flow sheets are shown for: petroleum refining, production of alcohol, butanol and acetone, glycerin, cellulose nitrate, cellulose acetate, coal tar products, nitrobenzene, aniline, indigo.

\* From *Process Industries Flow Sheets and Data Book*, by permission of the publishers, McGraw-Hill Publishing Company. See also *Process Industries Pictured Flow Sheets*, Chem. and Met. Eng., 1942.



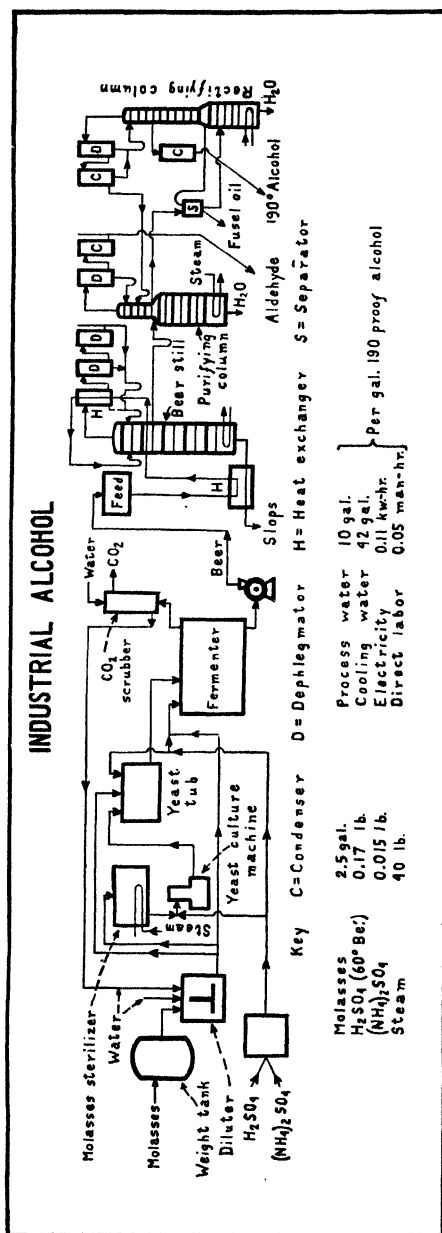


FIG. 106.

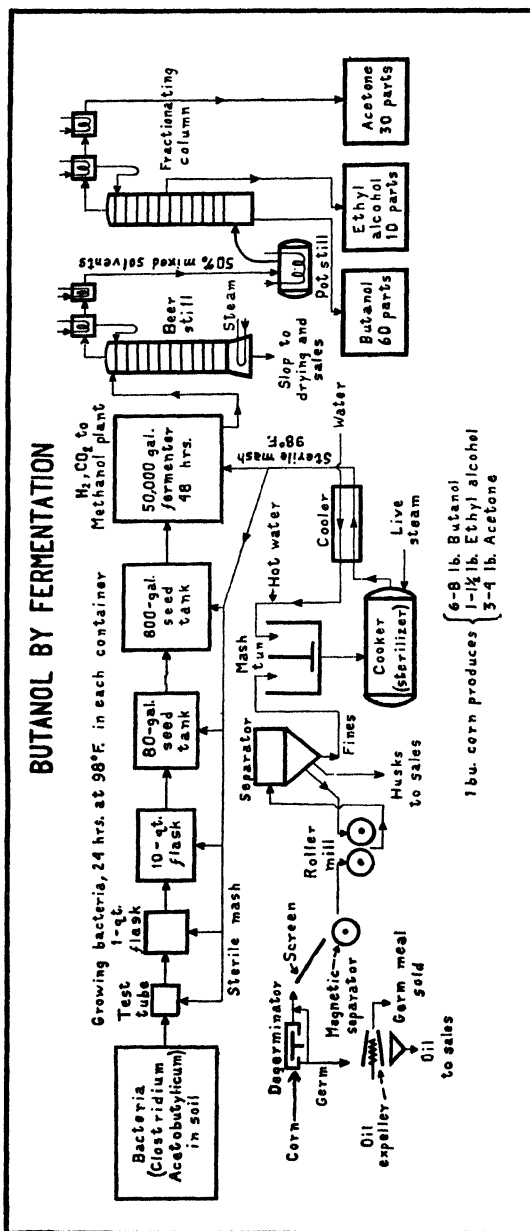


FIG. 107.

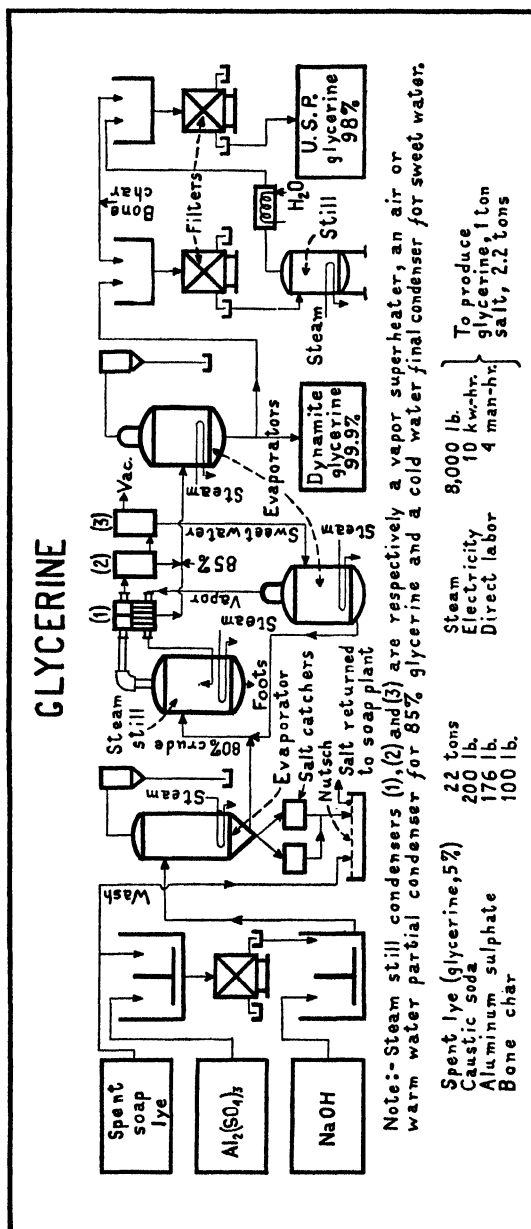


Fig. 108.



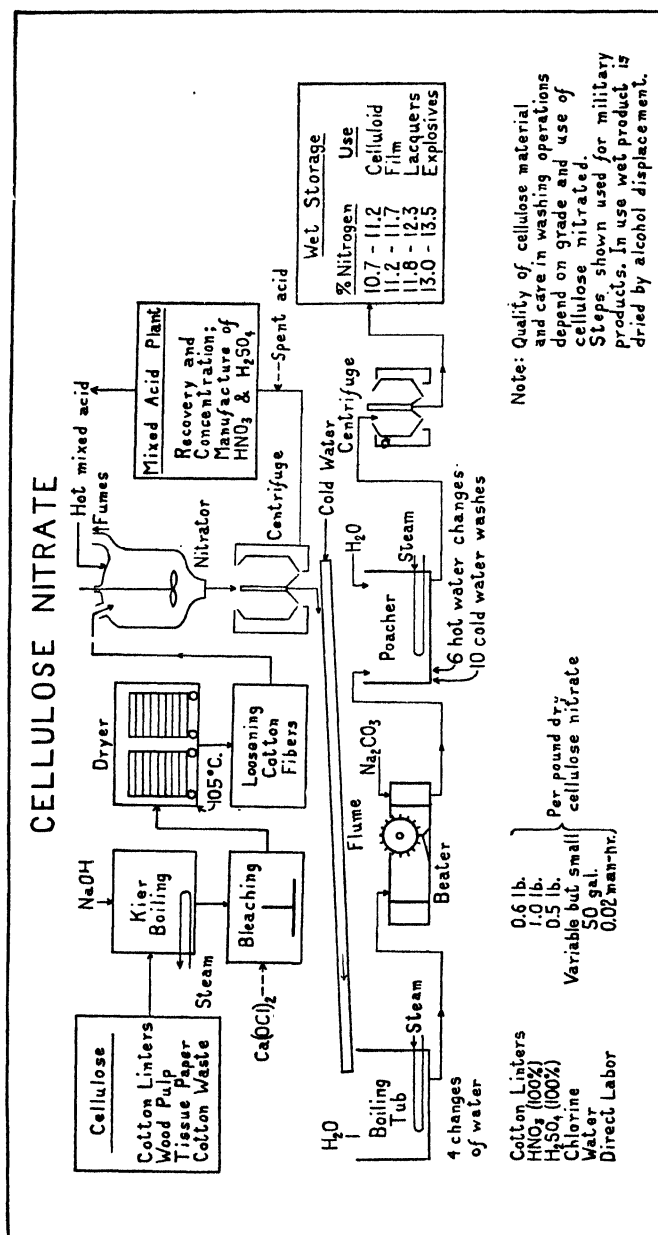


Fig. 109.

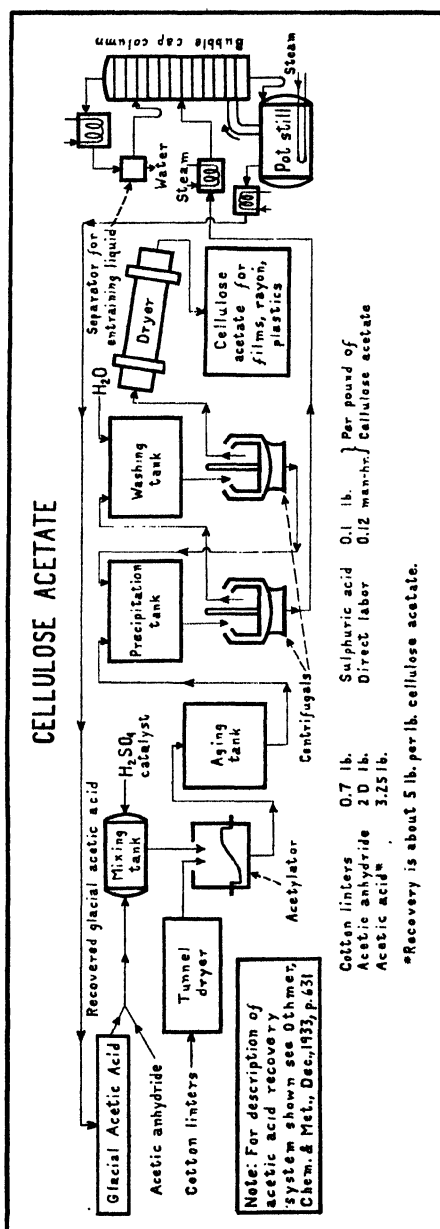


Fig. 110.



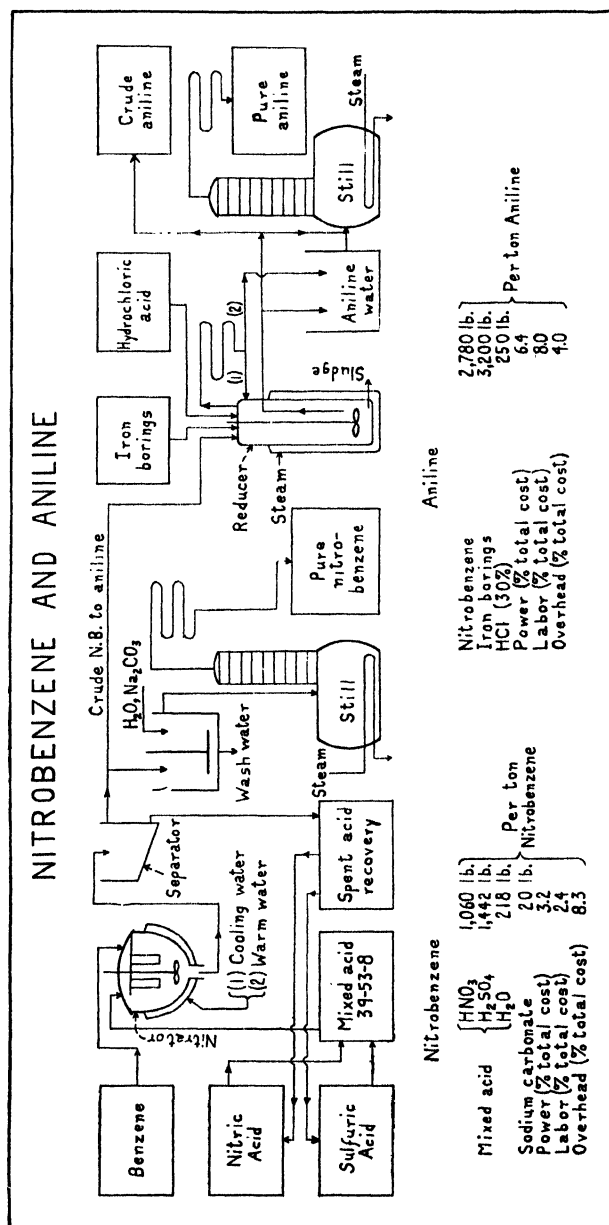


Fig. 112.

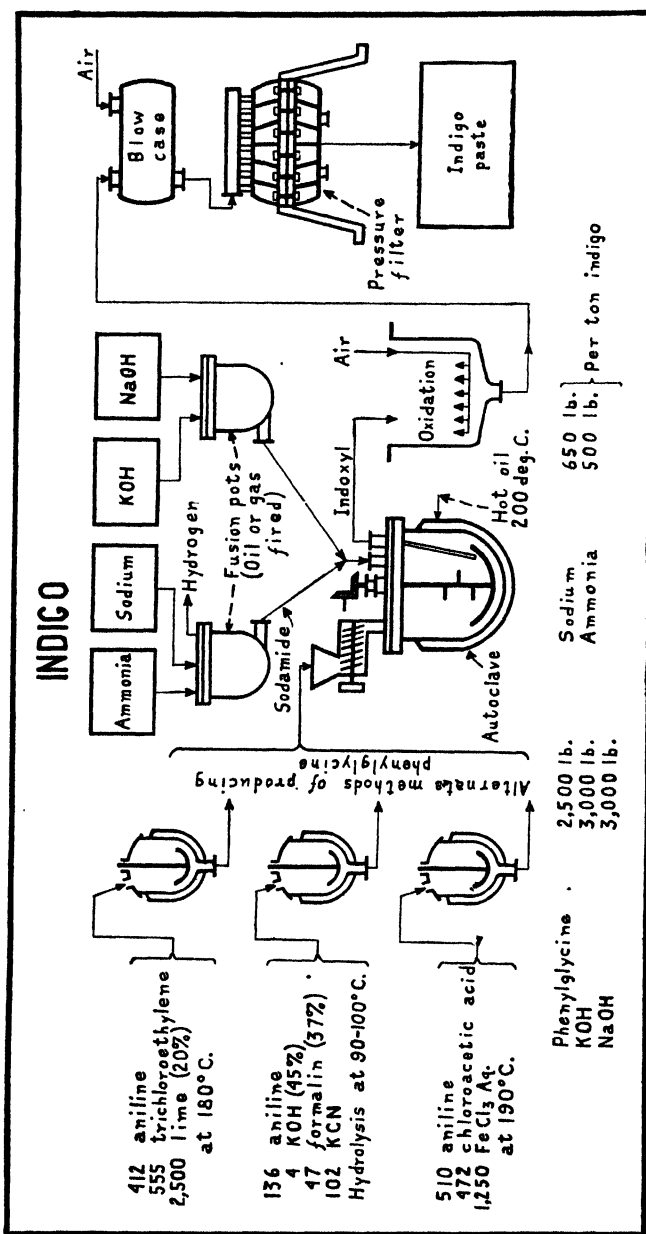


Fig. 113.

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*Abbreviations.* ft = reference to a footnote. t = reference to a table or chart.

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